

Analysis of the family of angiogenesis models with distributed time delays

Bodnar, M.^{*,1} & Piotrowska, M.J.^{*,2}

^{*}*Institute of Applied Mathematics and Mechanics,
University of Warsaw, Banacha 2, 02-097 Warsaw, Poland*

¹mbodnar@mimuw.edu.pl, ²monika@mimuw.edu.pl

Research Article

Contents

1	Introduction	2
2	Family of angiogenesis models with distributed delays	4
3	Mathematical analysis of family of angiogenesis models with distributed delays	5
3.1	Existence and uniqueness	5
3.2	Stability and Hopf bifurcations	7
3.2.1	Erlang probability densities	8
3.2.2	Piecewise linear probability densities	13
4	Stability results for parameters estimated by Hahnfeldt <i>et al.</i>	16
4.1	Erlang probability densities	17
4.2	Piecewise linear distributions	20
5	Discussion	21
A	Generalized Mikhailov Criterion	24
B	Acknowledgements	25

Abstract

In the presented paper a family of angiogenesis models, that is a generalisation of the Hahnfeldt *et al.* model is proposed. Considered family of models consists of two differential equations with distributed time delays. The global existence and the uniqueness of the solutions are proved. Moreover, the stability of the unique positive steady state is examined in the case of Erlang and piecewise linear delay distributions. Theorems guaranteeing the existence of stability switches and occurrence of Hopf bifurcations are proved. Theoretical results are illustrated by numerical analysis performed for parameters estimated by Hahnfeldt *et al.* (*Cancer Res.*, 1999).

Keywords: delay differential equations, distributed delay, stability analysis, Hopf bifurcation, angiogenesis

1 Introduction

Angiogenesis is a very complex process which accompanies us through our whole life starting from the development of the embryo and ending with wound healing in an advanced age since it is a process of blood vessels formation from pre-existing structures. Clearly, it is often considered as a vital process involved in organism growth and development. On the other hand, it can also be a pathological process since it may promote the growth of solid tumours. Indeed, in the first stage of solid tumour development cells create multicellular spheroid (MCS) — a small spherical aggregation. For a fast growing tumour (comparing to the healthy tissue) tumour's cells located in the centre of MCS receive less and less nutrients (such as glucose and oxygen) since they are only supplied through the diffusion of that substances from the external vessels. Hence, when MSC reaches a certain size (usually around 2–3 mm in diameter, [1,2]) two processes are observed: the saturation of growing cellular mass, and the formation of necrotic core in the centre of MCS. The tumour cells that are poorly nourished secrete number of angiogenic factors, e.g. FGF, VEGF, VEGFR, Ang1 and Ang2, which promote the proliferation and the differentiation of endothelial cells, smooth muscle cells, fibroblasts and also stabilise new created vessels initiating the process of angiogenesis. From that point of view, angiogenesis can be also considered as an essential step in the tumours transition from less harm for hosts avascular forms to cancers that are able to metastasise and finally cause the lethal outcome of the disease.

In [1] Folkman showed that the growth of solid tumours strongly depends on the amount of blood vessels that are induced to grow by tumours. He summarised that, if the tumour could be stopped from its own blood supply, it would wither and die, and nowadays he is considered as a father of an anti-angiogenic therapy the approach that aims to prevent the tumour from developing its own blood supply system.

On the other hand, angiogenesis has also an essential role in the tumours treatment during chemotherapy since anti-cancer drugs distributed with blood need to be delivered to the tumour and efficiently working vessels net allows the drugs to penetrate better the tumour structure. One also needs to take into account the fact that the vessel's net developed due to angiogenesis initiated by tumour cells is not as efficient as the net in healthy tissue e.g. consists of loops. That causes large difficulties during the treatment of tumours because drugs transport is often ineffective. Because of the reasons explained above, the process of angiogenesis is very important for the solid tumour growth and also for the anti-tumour treatment. Hence, a number of authors described that process using various mathematical models: macroscopic [3–11], individual-based models [12, 13] or hybrid models [14, 15]. One of the most well recognised angiogenesis models was proposed by Hahnfeldt *et al.* [11] later on studied in [8]. Among others, models with discrete delays describing the same angiogenesis process were recently considered in [5] and [16]. Models investigating the tumour development and angiogenesis in the context of anti-angiogenic therapy, chemotherapy or radiotherapy were also considered in [17–23], in the context of optimal treatment schedules [24–29] or in context of vessels maturation in [30, 31].

Let consider the family of the angiogenesis models that consists of two differential equations in the following form

$$\frac{d}{dt}p(t) = rp(t)h\left(\frac{p(t-\tau_1)}{q(t-\tau_1)}\right), \quad (1.1a)$$

$$\frac{d}{dt}q(t) = q(t)\left(b\left(\frac{p(t-\tau_2)}{q(t-\tau_2)}\right)^\alpha - a_H p^{2/3}(t) - \mu\right), \quad (1.1b)$$

where variables $p(t)$ and $q(t)$ represent the tumour volume at time t , and the maximal tumour size for which tumour cells can be nourished by the present vasculature. Thus, the ratio $\frac{p}{q}$ is interpreted as the measure of vessels density. The function h reflects dependence of tumour growth rate on the vascularisation. We assume h is decreasing. In the literature, in the context of model (1.1), it is usually

assumed that the tumour growth is governed by logistic, generalised logistic (see [8–10]) or by Gompertzian (see [8, 11]) law. The parameter r reflects the maximal tumour growth rate. The delays τ_1 and τ_2 present in the system represent time lags in the processes of the tumour growth and the vessels formation, respectively. Moreover, it is assumed that the population of the endothelial cells depends on both: the stimulation process initiated by poorly nourished tumour cells and the inhibiting factors secreted by tumour cells causing the lost of vessels. The parameter α reflects the strength of the dependence of the vessel dynamics on the ratio $\frac{p}{q}$. Parameters a_H and b are proportionality parameters of inhibition and stimulation of the angiogenesis process, respectively. We consider two processes, of which one appears on the surface of a sphere and the other the inside the sphere, and due to the spherical symmetry assumption we suppose that the ratio of the surface process depends proportionally to the tumour surface and it is represented by the exponent $2/3$. Thus, the term $-a_H q(t) p^{\frac{2}{3}}(t)$ appears in Eq. (1.1b). In model (1.1) the spontaneous loss of functional vasculature is represented by the term $-\mu q(t)$. In [11], the parameter μ was estimated to be equal to zero. On the other hand, the term $-\mu q(t)$ for $\mu > 0$ can be also interpreted as a constant continuous anti-angiogenic treatment, hence it is also considered in the presented study. For detailed derivation of system (1.1) without delays and with logarithmic function h from a reaction-diffusion system see [11].

Model (1.1) with Gompertzian tumour growth, $\alpha = 1$, and without time delays was firstly proposed by Hahnfeldt *et al.* in [11]. The modification of the Hahnfeldt *et al.* model was considered by various authors. d’Onofrio and Gandolfi [8] proposed system of ordinary differential equations (ODEs) based on Hahnfeldt *et al.* idea but with h being linear or logarithmic function, and with $\alpha = 0$, that is when the dynamics of the second variable of the model does not depend on the vascularisation of the tumour. Later in [32] Bodnar and Forys introduced discrete time delays into the model with the Gompertzian tumour growth and the family of models for parameter α from the interval $[0, 1]$ was considered. The analysis was later extended in [17]. In the same time, d’Onofrio and Gandolfi in [10] studied the model for $\alpha = 0$ with discrete time delays and different functions h . The analysis of the family of the models with discrete delays and the Gompertzian tumour growth was extended in [33, 34] where the directions of the existing Hopf bifurcations were studied.

However, in all these papers only discrete time delays were considered. One of the reasons is the fact that mathematical analysis of such models is easier than the models with distributed delays. Of course, in reality the duration of a process is never constant and it usually fluctuates around some value. Thus, we believe that delay is somehow distributed around some average value. This is the main reason why in this paper we study the modification of the family of models (1.1) in which the delays are distributed around their average values τ_1 and τ_2 instead of being concentrated in these points. On the other hand, we should also point out, that it might be difficult to estimate a particular delay distribution form experimental data.

Up to our knowledge such modification of the family of models has not been considered yet. We are also not aware of any result considering linear systems similar to the linearised system of the model with distributed delays considered in this paper. In fact known analytical results regarding the stability of trivial steady state for linear equations with distributed delays are rather limited, see e.g. [35] and references therein. Most results concern a single equation (see [36–38], and references therein). In some papers a second order equation or a system of equations with distributed delays are considered (see [39] for the second order linear equation, and [40] for the Lotka-Volterra system). However, in these two cases the time delays are only finite and the delayed terms do not appear on the diagonal of the stability matrix, and hence these results cannot be applied directly to the system considered in this paper. The single infinite distributed time delay is considered in [41] for the model of immune system–tumour interactions, however in that paper only an exponential distribution is considered and the linear chain trick that reduces the system with infinite delay to a larger system of ODEs is used.

A part of our results is based on application of the Mikhailov Criterion, which generalised version is formulated and proved in the Appendix. This generalisation plays an essential role in studying local

stability of the steady state with certain distributed delays.

The paper is organised as follows: in Section 2 considered family of angiogenesis models with distributed delays is proposed, and a proper phase space and initial conditions are defined. In Section 3 the mathematical analysis including the global existence and uniqueness of solutions, the stability of the existing steady state of considered family of models for different types of considered delay distributions is presented. In that section we also discuss possibilities of stability changes of the positive steady state. Next, our stability results are illustrated and extended by numerical simulations. In Section 5 we discuss and summary our results. Finally, for completeness in A we formulate generalized Mikhailov Criterion used in the paper and we prove it.

2 Family of angiogenesis models with distributed delays

The effect of the tumour stimulation of the vessels growth as well as the positive influence of the vessel network on the tumour dynamics is neither instantaneous nor delayed by some constant value. Hence, to reflect reality better, instead of constant delays considered earlier in [8], [33] or [34] we consider the delays that are distributed around some mean value and their distributions are given by the general probability densities f_i . We study the following system

$$\frac{d}{dt}p(t) = rp(t)h\left(\int_0^\infty f_1(\tau)\frac{p(t-\tau)}{q(t-\tau)}d\tau\right), \quad (2.1a)$$

$$\frac{d}{dt}q(t) = q(t)\left(b\int_0^\infty f_2(\tau)\left(\frac{p(t-\tau)}{q(t-\tau)}\right)^\alpha d\tau - a_H p^{2/3}(t) - \mu\right), \quad (2.1b)$$

where $f_i(s) : [0, \infty) \rightarrow \mathbb{R}_\geq$ are delay distributions with the following properties:

$$(H1) \quad \int_0^\infty f_i(s)ds = 1, i = 1, 2 \text{ and}$$

$$(H2) \quad 0 \leq \int_0^\infty sf_i(s)ds < \infty, i = 1, 2.$$

Moreover, we assume that the function h has the following properties:

(P1) $h : (0, \infty) \rightarrow \mathbb{R}$ is a continuously differentiable decreasing function;

(P2) $h(1) = 0$;

(P3) $h'(1) = -1$.

Note, that properties (P2) and (P3) do not make our studies less general as a proper rescaling and a suitable choice of parameter r always allows us to arrive to the case $h(1) = 0$ and $h'(1) = -1$. Note also, that an arbitrary probability distribution defined on $[0, +\infty)$ with a finite expectation fulfils assumptions (H1) and (H2).

To close model (2.1) we need to define initial conditions. We consider a continuous initial function $\phi : (-\infty, 0] \rightarrow \mathbb{R}^2$. For infinite delays we need to regulate the behaviour of this function as t tends to $-\infty$. To this end, we introduce a suitable space. Let us denote as $C = C((-\infty, 0], \mathbb{R}^2)$ the space of continuous functions defined on the interval $(-\infty, 0]$ with values in \mathbb{R}^2 . For an arbitrary chosen non-decreasing continuous function $\eta : (-\infty, 0] \rightarrow \mathbb{R}^+$ such that $\lim_{\theta \rightarrow -\infty} \eta(\theta) = 0$, we define the Banach space

$$\mathcal{K}_\eta = \left\{ \varphi \in C : \lim_{\theta \rightarrow -\infty} \varphi(\theta)\eta(\theta) = 0 \quad \text{and} \quad \sup_{\theta \in (-\infty, 0]} |\varphi(\theta)\eta(\theta)| < \infty \right\},$$

with a norm

$$\|\varphi\|_\eta = \sup_{\theta \in (-\infty, 0]} |\varphi(\theta)\eta(\theta)|, \quad \text{for any } \varphi \in \mathcal{K}_\eta.$$

We need initial functions ϕ to be in \mathcal{K}_η for some arbitrary non-decreasing continuous function η that tends to 0 for arguments tending to $-\infty$ (see [42]). If the delay is finite, that is if supports of f_1 and f_2 are compact, we suppose initial functions $\phi \in \mathbf{C}([-\tau_{\max}, 0], \mathbb{R}^2)$, where the interval $[-\tau_{\max}, 0]$ contains supports of f_i , $i = 1, 2$. However, this is equivalent to consideration of the space \mathcal{K}_η with an arbitrary η being equal to 1 on $[-\tau_{\max}, 0]$ and decreasing to 0 in $-\infty$. If the support of the probability density is unbounded and the initial function ϕ is also unbounded, then we need to choose an appropriate function η (which in turn implies a choice of the phase space \mathcal{K}). The function η must be chosen to control the behaviour of the initial function in $-\infty$. However, due to biological interpretation of the model parameter, it is reasonable to restrict our analysis to the globally bounded initial functions. Thus, we can choose an arbitrary positive continuous non-decreasing function η such that $\eta(\theta) \rightarrow 0$ for $\theta \rightarrow -\infty$ for example $\eta = e^\theta$. Nevertheless, because such assumption would not make theorems' formulation simpler, we decided to present and prove theorems for arbitrary initial functions and not to assume a particular form of the function η .

3 Mathematical analysis of family of angiogenesis models with distributed delays

Due to properties **(P2)** and **(H1)** the steady states of system (2.1) are the same as for Hahnfeldt *et al.* and d'Onofrio-Gandolfi models without delays or with discrete delays. Thus, system (2.1) has a unique positive steady state (p_e, q_e) , where $p_e = q_e = \left(\frac{b-\mu}{a_H}\right)^{\frac{3}{2}}$ (compare e.g. [33]) if and only if $b > \mu$. Hence, in the rest of the paper we assume that $b > \mu$ holds.

Note, that solution to the equations defined by (2.1) can be written in the exponential form. Thus, using the same argument as in [10] or in [33] (for the discrete delay cases), we deduce that \mathbb{R}_+^2 is the invariant set for system (2.1).

Note, that in system (2.1) terms with delay are of the form p/q . This, together with the invariance of \mathbb{R}_+^2 suggests the following change of variables

$$x = \ln\left(\frac{p}{p_e}\right), \quad y = \ln\left(\frac{pq_e}{qp_e}\right)$$

giving

$$\begin{aligned} \frac{d}{dt}x(t) &= rh \left(\int_0^\infty f_1(\tau) e^{y(t-\tau)} d\tau \right), \\ \frac{d}{dt}y(t) &= rh \left(\int_0^\infty f_1(\tau) e^{y(t-\tau)} d\tau \right) - b \int_0^\infty f_2(\tau) e^{\alpha y(t-\tau)} d\tau + (b - \mu) e^{\frac{2}{3}x(t)} + \mu. \end{aligned} \quad (3.1)$$

Newly introduced variable y allows us to consider the system where only one variable (y) has delayed argument, whereas in system (2.1) both variables have delayed arguments. Clearly, the steady state for re-scaled system (3.1) is $(x_e, y_e) = (0, 0)$.

It should be mentioned here that the scaling procedure transforms \mathbb{R}_+^2 into the whole \mathbb{R}^2 , so space \mathcal{K}_η is the appropriate phase space for the model (3.1).

3.1 Existence and uniqueness

Proposition 3.1 *Let $\eta : (-\infty, 0] \rightarrow \mathbb{R}^+$ be a continuous, non-decreasing function such that $\lim_{\theta \rightarrow -\infty} \eta(\theta) = 0$, let functions f_i fulfil **(H1)**–**(H2)**, and let function h fulfils **(P1)**–**(P3)**. For an arbitrary initial function $\phi = (\phi_1, \phi_2) \in \mathcal{K}_\eta$ there exists $t_\phi > 0$ such that system (3.1) with initial condition $x(t) = \phi_1(t)$, $y(t) = \phi_2(t)$ for $t \in (-\infty, 0]$, has a unique solution in \mathcal{K}_η defined on $t \in [0, t_\phi)$.*

Proof : The right-hand side of system (3.1) fulfils a local Lipschitz condition. In fact, the assumption **(P1)** implies that the derivative of h is bounded on an arbitrarily chosen compact set of $(0, +\infty)$. Thus, the function h is locally Lipschitz continuous function as well as all functions on the right-hand side of (3.1). This implies that the Lipschitz condition is fulfilled for any bounded set in \mathcal{K}_η . Hence, there exists a unique solution to system (3.1) defined on $t \in [0, t_\phi)$ (see [42, Chapter 2, Theorem 1.2]). ■

Theorem 3.2 (global existence) *If assumptions of Proposition 3.1 are fulfilled, the probability densities f_i and an initial function are globally bounded, then solutions to (3.1) are defined for all $t \geq 0$.*

Proof : The right-hand side of (3.1) can be written in a functional form as

$$\frac{d}{dt}x(t) = G_1(x_t, y_t), \quad \frac{d}{dt}y(t) = G_2(x_t, y_t),$$

with

$$\begin{aligned} G_1(\phi_x, \phi_y) &= rh \left(\int_0^\infty f_1(\tau) e^{\phi_y(-\tau)} d\tau \right), \\ G_2(\phi_x, \phi_y) &= rh \left(\int_0^\infty f_1(\tau) e^{\phi_y(-\tau)} d\tau \right) - b \int_0^\infty f_2(\tau) e^{\alpha\phi_y(-\tau)} d\tau + (b - \mu) e^{\frac{2}{3}\phi_x(0)} + \mu, \end{aligned}$$

for $(\phi_x, \phi_y) \in \mathcal{C}$. Note that due to **(P1)** we have $|G_1(\phi_x, \phi_y)| \leq rh(\exp(-\|\phi_y\|))$ and similar inequality holds for $|G_2(\phi_x, \phi_y)|$. This implies, that the function (G_1, G_2) maps bounded sets of \mathcal{C} into bounded sets of \mathbb{R}^2 (so their closures are compact). Thus, if the solution to (3.1) cannot be prolonged beyond the interval $[0, T)$, for some finite T , then $\lim_{t \rightarrow T} (\|x_t\|_\eta + \|y_t\|_\eta) = +\infty$ (see [42, Chapter 2, Theorem 2.7]).

In the following, we show that x and y are bounded on $[0, T)$ hence, the solution exists for all $t \geq 0$.

Let $\delta > 0$ be an arbitrary number such that $\int_\delta^\infty f_i(\tau) d\tau > 0$ for $i = 1, 2$. Using the step method we choose the time step equal to δ and we show that the solution to (3.1) can be prolonged on the interval $[0, \delta]$ and hence on the interval $[n\delta, (n+1)\delta]$, for any $n \in \mathbb{N}$. Let letters C_i denote constants that will be chosen later in a suitable way.

First, we provide an upper bound of the solution. Due to boundedness of $y(t)$ for $t \leq 0$, we write

$$\int_0^\infty f_1(\tau) e^{y(t-\tau)} d\tau = \int_0^\delta f_1(\tau) e^{y(t-\tau)} d\tau + \int_\delta^\infty f_1(\tau) e^{y(t-\tau)} d\tau \geq \int_\delta^\infty f_1(\tau) e^{y(t-\tau)} d\tau \geq C_1,$$

for all $t \in [0, \delta]$. This estimation leads to a conclusion

$$\frac{d}{dt}x(t) \leq rh(C_1) \implies x(t) \leq C_2 \quad \text{for } t \in [0, \delta].$$

From the second equation of (3.1), arguing in a similar way, we have

$$\frac{d}{dt}y(t) \leq rh(C_1) + (b - \mu) e^{C_3} + \mu \implies y(t) \leq C_4, \quad \text{for } t \in [0, \delta].$$

Now, we proceed with a lower bound of the solutions. Splitting integral on the interval $(0, +\infty)$ into two integrals and using the fact that $y(t)$ is bounded we obtain

$$\begin{aligned} \int_0^\infty f_1(\tau) e^{y(t-\tau)} d\tau &= \int_0^\delta f_1(\tau) e^{y(t-\tau)} d\tau + \int_\delta^\infty f_1(\tau) e^{y(t-\tau)} d\tau \leq \int_0^\delta f_1(\tau) e^{y_M} d\tau + C_5 \\ &\leq \int_0^\infty f_1(\tau) e^{y_M} d\tau + C_5 \leq e^{y_M} + C_5 = C_6, \end{aligned}$$

where y_M is an upper bound of $y(t)$ on the interval $[-\tau, \delta - \tau]$. This estimation together with a similar argument applied to the second integral in the second equation of (3.1) yields

$$\int_0^\infty f_2(\tau) e^{\alpha y(t-\tau)} d\tau \leq C_7.$$

Therefore, from the second equation of (3.1) we have

$$\frac{d}{dt}y(t) \geq rh(C_6) - bC_7 \implies y(t) \geq C_8, \text{ for } t \in [0, \delta].$$

The boundedness of y together with the form of first equation of (3.1) implies boundedness of $x(t)$ on $[0, \delta]$. Now, knowing that $x(t)$ and $y(t)$ are bounded on the interval $(-\infty, \delta]$, an analogous reasoning allows us to deduce the boundedness of the solution on the interval $(-\infty, 2\delta]$. Hence, the mathematical induction yields the boundedness of the solutions to (3.1) on each compact interval included in $[0, +\infty)$, which completes the proof. ■

3.2 Stability and Hopf bifurcations

In this section we study the local stability of the steady state $(0,0)$ using standard linearisation technique. Linearisation of system (3.1) around the steady state $(0,0)$ has the following form

$$\begin{aligned} \frac{d}{dt}x(t) &= rh'(1) \int_0^\infty f_1(\tau)y(t-\tau) d\tau, \\ \frac{d}{dt}y(t) &= \frac{2}{3}(b-\mu)x(t) + \int_0^\infty (rh'(1)f_1(\tau) - abf_2(\tau))y(t-\tau) d\tau, \end{aligned} \quad (3.2)$$

and, due to the equality $h'(1) = -1$ (see Property **(P3)**), the corresponding characteristic function is given by

$$W(\lambda) = \det \begin{bmatrix} \lambda & r \int_0^\infty f_1(\tau) e^{-\lambda\tau} d\tau \\ -\frac{2}{3}(b-\mu) & \lambda + \int_0^\infty (rf_1(\tau) + abf_2(\tau)) e^{-\lambda\tau} d\tau \end{bmatrix}.$$

Thus,

$$W(\lambda) = \lambda^2 + \lambda \int_0^\infty (rf_1(\tau) + abf_2(\tau)) e^{-\lambda\tau} d\tau + \frac{2r}{3}(b-\mu) \int_0^\infty f_1(\tau) e^{-\lambda\tau} d\tau.$$

In general, as the probability densities one considers the specific distributions which describe the experimental data or studied phenomena in the best way. In the present paper, we consider two particular types of the probability densities. One type is given by

$$f_i(\tau) = \frac{1}{\varepsilon^2} \begin{cases} \varepsilon - \sigma + \tau, & \tau \in [\sigma - \varepsilon, \sigma), \\ \varepsilon + \sigma - \tau, & \tau \in [\sigma, \sigma + \varepsilon], \\ 0 & \text{otherwise.} \end{cases} \quad \text{for } \sigma \geq \varepsilon, i = 1, 2, \quad (3.3)$$

We call probability densities defined by (3.3) piecewise linear probability densities. Note, that for $\varepsilon \rightarrow 0$ the functions f_i converge to Dirac delta at the points σ and therefore, system (2.1) becomes a system with discrete delays considered by [8, 17, 33, 34]. Since we assume that all considered probability densities are defined on interval $[0, \infty)$ condition $\sigma \geq \varepsilon$ must be fulfilled. Note, that for $\sigma \geq \varepsilon$ the average value of f_i is equal to σ and the standard deviation is equal to $\varepsilon/\sqrt{6}$. For $\sigma < \varepsilon$ one obtains so-called neutral equations, for details see [43].

In this paper, we also consider second type of probability densities so-called the Erlang probability densities separated or not from zero by $\sigma \geq 0$, i.e. we study system (2.1) with functions given by

$$f_1(\tau) = g_{m_1}(\tau - \sigma), \quad f_2(\tau) = g_{m_2}(\tau - \sigma), \quad (3.4)$$

where $g_{m_i}(\tau)$, $i = 1, 2$, are called non-shifted Erlang distributions and are defined by

$$g_{m_i}(s) = \frac{a}{(m_i - 1)!} (as)^{m_i-1} e^{-as}, \quad (3.5)$$

with $a > 0$, $s \geq 0$. The mean value of the non-shifted Erlang distribution g_{m_i} is given by $\frac{m_i}{a}$, while the variance is equal to $\frac{m_i}{a^2}$. Hence, the average delay is equal to this mean and the deviation $\sqrt{\frac{m_i}{a^2}}$ measures the degree of concentration of the delays about the average delay. Clearly, the non-shifted Erlang distribution is a special case of the Gamma distribution, where the shape parameter m_i is an integer. It is also easy to see that the non-shifted Erlang distribution is the generalisation of the exponential distribution, which one gets taking $m_i = 1$. On the other hand, for the non-shifted Erlang distributions when $m_i \rightarrow +\infty$ the probability densities g_{m_i} converge to a Dirac distributions and hence the system with discrete delays (1.1) is recovered as a limit of Erlang distributions for system (2.1). For the shifted Erlang distribution the mean value is $\sigma + \frac{m}{a}$, while variances stay the same as for the non-shifted case.

3.2.1 Erlang probability densities

The Erlang probability densities separated from zero by σ read

$$f_i(\tau) = \frac{a^{m_i}(\tau - \sigma)^{m_i-1}}{(m_i - 1)!} e^{-a(\tau - \sigma)}, \quad \text{for } \tau \geq \sigma$$

and 0 otherwise, for $i = 1, 2$. Note, that in this paper we consider only the case $a > 0$. Then for probability densities given by (3.4)–(3.5) we have

$$\int_0^\infty f_i(\tau) e^{-\lambda\tau} d\tau = \frac{a^{m_i}}{(a + \lambda)^{m_i}} e^{-\lambda\sigma}.$$

Hence, the characteristic function has the following form

$$W(\lambda) = \lambda^2 + \lambda \left(r \frac{a^{m_1}}{(a + \lambda)^{m_1}} e^{-\lambda\sigma} + \alpha b \frac{a^{m_2}}{(a + \lambda)^{m_2}} e^{-\lambda\sigma} \right) + \frac{2r}{3}(b - \mu) \frac{a^{m_1}}{(a + \lambda)^{m_1}} e^{-\lambda\sigma}. \quad (3.6)$$

Define

$$\beta = r + \alpha b \quad \text{and} \quad \gamma = \frac{2r(b - \mu)}{3}. \quad (3.7)$$

Proposition 3.3 *Let $b > \mu$. The trivial steady state of system (3.1) with the non-shifted Erlang probability density given by (3.4)–(3.5) ($\sigma = 0$) is locally asymptotically stable if*

- (i) $a\beta > \gamma$ for $m_1 = m_2 = 1$;
- (ii) $a > \frac{1}{2}\beta + \frac{2\gamma}{\beta}$ for $m_1 = m_2 = 2$;
- (iii) $a > \frac{9}{8}\beta$ and $8\beta a^3 - 3(8\gamma + 3\beta^2)a^2 + 3\gamma\beta a - \gamma^2 > 0$ for $m_1 = m_2 = 3$;
- (iv) $2a(a + r) > (a(a + \alpha b) + \gamma) + \frac{4a^2\gamma}{(a(a + \alpha b) + \gamma)}$ for $m_1 = 1$ and $m_2 = 2$;
- (v) $a > \frac{1}{2}\beta + \frac{2\gamma}{\beta} - \alpha b$ for $m_1 = 2$ and $m_2 = 1$.

Proof : For $\sigma = 0$ we clearly have

$$W(\lambda) = \lambda^2 + \lambda \left(r \frac{a^{m_1}}{(a + \lambda)^{m_1}} + \alpha b \frac{a^{m_2}}{(a + \lambda)^{m_2}} \right) + \frac{2r}{3}(b - \mu) \frac{a^{m_1}}{(a + \lambda)^{m_1}}.$$

As it can be seen, the advantage of using the Erlang distributions (not separated from zero) is that instead of studying existence of the zeros of the characteristic function one can study existence of roots of a polynomial, thus the stability analysis is easier.

First, consider $m_1 = m_2 = m$. We investigate the behaviour of the roots of polynomial

$$\lambda^2(a + \lambda)^m + a^m(\lambda\beta + \gamma), \quad (3.8)$$

where β and γ are given by (3.7).

The Routh-Hurwitz stability criterion (see eg. [44]) gives that the necessary and sufficient conditions for the stability of trivial steady state of system (3.2). Clearly, the degree of polynomial (3.8) is larger for larger m . However, in each case of equals m 's (sometimes tedious) algebraic calculations lead to some conditions that guarantee the stability of the considered steady state.

For $m = 1$ (i.e. for the exponential distribution not separated from zero) we have a polynomial of degree three

$$\lambda^2(a + \lambda) + a(\lambda\beta + \gamma),$$

while for $m = 2$ we have

$$\lambda^4 + 2a\lambda^3 + a^2\lambda^2 + \beta a^2\lambda + \gamma a^2.$$

The case $m = 3$, is the most complicated since a direct calculation shows that (3.8) is the polynomial of degree 5

$$\lambda^5 + 3a\lambda^4 + 3a^2\lambda^3 + a^3\lambda^2 + a^3\beta\lambda + a^3\gamma.$$

For $m_1 = 1$ and $m_2 = 2$, polynomial (3.8) reads

$$\lambda^4 + 2a\lambda^3 + a(a + r)\lambda^2 + (a^2\beta + \gamma a)\lambda + \gamma a^2,$$

while for $m_1 = 2$ and $m_2 = 1$ we have

$$\lambda^4 + 2a\lambda^3 + a(a + \alpha b)\lambda^2 + a^2\beta\lambda + \gamma a^2.$$

■

Proposition 3.4 For $b > \mu$, $\sigma = 0$, $m_1 = 1$, $m_2 = 2$ and

$$r < \alpha b \quad \text{or} \quad r > \frac{\alpha b}{2} + \frac{2\gamma}{\alpha b}, \quad (3.9)$$

there exists $\bar{a} > 0$ such that for $a > \bar{a}$ the trivial steady state of system (3.1) with the non-shifted Erlang probability densities given by (3.4)–(3.5) is locally asymptotically stable and it is unstable for $a \in (0, \bar{a})$.

Proof : Since $a(a + \alpha b) + \gamma > 0$ holds, the stability condition for the case $m_1 = 1$, $m_2 = 2$ (the condition (ii) of Theorem 3.3) is equivalent to

$$W_a(a) = a^4 + 2ra^3 + (\alpha b(2r - \alpha b) - 4\gamma)a^2 + 2\gamma(r - \alpha b)a - \gamma^2 > 0.$$

The Descart's rule of signs implies that if one of conditions (3.9) holds, then there exists exactly one simple positive real root of $W_a(a)$. We denote it by \bar{a} . Then the trivial steady state system (3.1) is locally asymptotically for $a > \bar{a}$ and unstable for $0 < a < \bar{a}$. ■

Theorem 3.5 Considered system (3.1) with the shifted Erlang probability densities given by (3.4)–(3.5).

(a) Let $m_i = m$, $i = 1, 2$. If the trivial steady state is

(i) unstable for $\sigma = 0$, then it is unstable for any $\sigma > 0$,

- (ii) *locally asymptotically stable for $\sigma = 0$, then there exists $\sigma_0 > 0$ such that it is locally stable for all $\sigma \in [0, \sigma_0)$ and unstable for $\sigma > \sigma_0$. At $\sigma = \sigma_0$ the Hopf bifurcation occurs.*
- (b) *Let $m_1 = 1, m_2 = 2$. If the trivial steady state is locally asymptotically stable for $\sigma = 0$, then there exists exactly one $\sigma_0 > 0$ such that for $\sigma \in [0, \sigma_0)$ it is locally asymptotically stable and it is unstable for $\sigma > \sigma_0$. At $\sigma = \sigma_0$ the Hopf bifurcation occurs.*
- (c) *Let $m_1 = 2, m_2 = 1$.*

(i) *If the steady state is locally asymptotically stable for $\sigma = 0$, and the function*

$$F(u) = u^4 + 2a^2u^3 + u^2a^2(a^2 - \alpha^2b^2) - ua^3(a\beta^2 - 2\alpha b\gamma) - \gamma^2a^4. \quad (3.10)$$

has no positive multiple roots, then the steady state is locally asymptotically stable for some $\sigma \in [0, \sigma_0)$ and it is unstable for $\sigma > \bar{\sigma}$, with $\sigma_0 \leq \bar{\sigma}$. At $\sigma = \sigma_0$ the Hopf bifurcation occurs.

(ii) *If*

$$a \geq \alpha b \min \left\{ 1, \frac{2\gamma}{\beta^2} \right\}, \quad (3.11)$$

or

$$a < \alpha b \min \left\{ 1, \frac{2\gamma}{\beta^2} \right\} \text{ and } (a^2 + 2\alpha^2b^2)^3 < 27(2\alpha b\gamma + a(\alpha^2b^2 - \beta^2))^2, \quad (3.12)$$

then at most one stability switch of the steady state is possible. Moreover, if the steady state is locally asymptotically stable for $\sigma = 0$, then it is stable for some $\sigma \in [0, \sigma_0)$ and it is unstable for $\sigma > \sigma_0$. For $\sigma = \sigma_0$ the Hopf bifurcation is observed.

Proof : Let $m_M = \max\{m_1, m_2\}$. Then the characteristic function (3.6) has the following form

$$W(\lambda) = \frac{1}{(a + \lambda)^{m_M}} \left(\lambda^2(a + \lambda)^{m_M} + \left(\lambda(ra^{m_1}(a + \lambda)^{m_M-m_1} + \alpha ba^{m_2}(a + \lambda)^{m_M-m_2}) + \gamma a^{m_1}(a + \lambda)^{m_M-m_1} \right) e^{-\lambda\sigma} \right).$$

The zeros of $W(\lambda)$ are the same as the zeros of

$$D(\lambda) = \lambda^2(a + \lambda)^{m_M} + \left(\lambda(ra^{m_1}(a + \lambda)^{m_M-m_1} + \alpha ba^{m_2}(a + \lambda)^{m_M-m_2}) + \gamma a^{m_1}(a + \lambda)^{m_M-m_1} \right) e^{-\lambda\sigma}. \quad (3.13)$$

For $\lambda = i\omega$ define an auxiliary function

$$F(\omega) = \omega^4(a^2 + \omega^2)^{m_M} - \left\| i\omega(ra^{m_1}(a + i\omega)^{m_M-m_1} + \alpha ba^{m_2}(a + i\omega)^{m_M-m_2}) + \gamma a^{m_1}(a + i\omega)^{m_M-m_1} \right\|^2. \quad (3.14)$$

In the following we show, with one exception, that there exists a unique single positive zero $\omega_0 = \sqrt{u_0}$ of the function F such that $F'(\omega_0) > 0$. This, together with Theorem 1 from [45] allows us to deduce that the zeros of D crosses imaginary axes from left to right with a positive velocity. This yields the existence of stability switches and the occurrence of the Hopf bifurcation in the appropriate cases.

For $m_1 = m_2 = m$, and for $u = \omega^2$ the auxiliary function F takes the form

$$F(u) = u^2(a^2 + u)^m - a^{2m}(u\beta^2 + \gamma^2). \quad (3.15)$$

We are interested in the existence of the real positive roots of (3.15). Because the number of sign changes between consecutive non-zero coefficients is equal to 1 the Descartes' rule of signs indicates

that the polynomial (3.15) has one simple real positive root denoted by u_0 . Clearly, the fact that coefficient of u^{2+m} is positive and $F(0) < 0$, implies $F'(u_0) \geq 0$.

Moreover,

$$F'(u) = 2u(a^2 + u)^m + mu^2(a^2 + u)^{m-1} - a^{2m}\beta^2$$

and thus, $F''(u) > 0$. Hence, $F'(u_0) > 0$. This completes the proof of part (a).

For $m_1 = 1$, $m_2 = 2$ and $u = \omega^2$ the function F given by (3.14) has the form

$$F(u) = u^4 + 2a^2 u^3 + a^2(a^2 - r^2)u^2 - a^2(a^2\beta^2 + 2a\alpha b\gamma + \gamma^2)u - a^4\gamma^2. \quad (3.16)$$

We show that the coefficient of u in (3.16) is negative and hence the Descartes' rule of signs implies that a single stability switch for the trivial steady state of (3.1) occurs. This is equivalent to the inequality

$$G(a) = a^2\beta^2 + 2a\alpha b\gamma + \gamma^2 > 0,$$

for $a \geq 0$. For $b > \mu$ (that is the condition required for the existence of the trivial steady state of (3.1)) the discriminant of G is the following

$$4\gamma^2(\alpha^2 b^2 - \beta^2) = 4\gamma^2(\alpha^2 b^2 - (r + \alpha b)^2) = -4r\gamma^2(r + 2\alpha b) < 0.$$

Thus, $G(u) > 0$, so F has exactly one simple positive root u_0 . Moreover, $F(0) < 0$ hence $F'(u_0) > 0$ and the proof of part (b) is completed.

Consider the case: $m_1 = 2$ and $m_2 = 1$. Then for $u = \omega^2$ Eq. (3.14) takes the form (3.10) First, note that for the auxiliary function given by (3.10) inequality $F(0) < 0$, holds. Thus, F has at least one real positive zero. Hence, if F has only simple positive zero, by Theorem 1 from [45] the steady state of system (3.1) is unstable for sufficiently large σ , which completes the proof of part (c.i).

Now, we prove statement (c.ii). Assume that (3.11) holds. Then, if $a \geq \alpha b$, then the coefficient of u^2 is non-negative and independently on the sign of the coefficient of u the Descartes' rule of signs indicates that there is exactly one simple positive real zero of $F(u)$. Thus, at most one stability switch of the steady state can occur. On the other hand, if condition $a \geq 2\alpha\gamma b/\beta^2$ holds, then the coefficient of u in $F(u)$ is non-positive. Hence, independently of the sign of the coefficient of u^2 the single change of the sign is observed. Thus, $F(u)$ has exactly one simple real positive zero.

Now assume that (3.12) holds. To shorten notation denote

$$\alpha_1 = 2\alpha b\gamma - a\beta^2, \quad \alpha_2 = a^2 b^2 - a^2. \quad (3.17)$$

The first inequality of (3.12) is equivalent to $\alpha_1 > 0$ and $\alpha_2 > 0$. Denote $F_1(\zeta) = F(a\zeta)/a^4$, with $\zeta = u/a$. Clearly, $F(u) = 0$ is equivalent to $F_1(\zeta) = 0$. The function F_1 reads

$$F_1(\zeta) = \zeta^4 + 2a\zeta^3 - \alpha_2\zeta^2 + \zeta\alpha_1 - \gamma^2.$$

We show that under the assumption (3.12) the function F_1 is a strictly monotonic function of ζ , which implies that F is a strictly monotonic function of u . This, together with the fact $F(0) < 0$ implies that F has exactly one simple positive zero so the assertion of the point (c.ii) is true.

In order to show monotonicity of F_1 , we prove that its first derivative is positive. We have

$$F'_1(\zeta) = 4\zeta^3 + 6a\zeta^2 - 2\alpha_2\zeta + \alpha_1.$$

The assumption $\alpha_1 > 0$ implies $F'_1(0) > 0$. Now, we derive a condition that guarantees the positivity of F'_1 for all $\zeta > 0$. To this end, we calculate the minimum of $F'_1(\zeta)$ on the interval $[0, +\infty)$. Calculating the second derivative of F_1 we find that the minimum of F'_1 is reached at the point

$$\bar{\zeta} = \frac{1}{2} \left(-a + \sqrt{a^2 + \frac{2}{3}\alpha_2} \right).$$

Using the fact that $F_1''(\bar{\zeta}) = 0$ we have

$$F_1'(\bar{\zeta}) = \alpha_1 - 2\bar{\zeta}^3 - \alpha_2\bar{\zeta}.$$

Thus, F_1 is strictly increasing for all $\zeta > 0$ if and only if

$$(2\bar{\zeta}^2 + \alpha_2)\bar{\zeta} < \alpha_1. \quad (3.18)$$

A few algebraic manipulations indicate that (3.18) is equivalent to

$$\left(a^2 + \frac{2}{3}\alpha_2\right)^{3/2} - a(a^2 + \alpha_2) < \alpha_1.$$

Using the definition of α_2 the above inequality reads

$$\frac{1}{3\sqrt{3}}(a^2 + 2\alpha^2 b^2)^{3/2} < \alpha_1 + a\alpha^2 b^2.$$

Due to the assumption $\alpha_1 > 0$ both sides of the above inequality are positive, so squaring that inequality we obtain

$$(a^2 + 2\alpha^2 b^2)^3 < 27(\alpha_1 + a\alpha^2 b^2)^2.$$

Now using the definition of α_1 we get

$$(a^2 + 2\alpha^2 b^2)^3 < 27(2\alpha b\gamma + a(\alpha^2 b^2 - \beta^2))^2,$$

which is fulfilled due to the second inequality of (3.12). This completes the proof of part (c). \blacksquare

Note, that there exist a set of parameters of system (3.1) with the shifted Erlang probability densities given by (3.4)–(3.5) with $m_1 = 2$, $m_2 = 1$ such that the steady state is locally asymptotically stable for $\sigma = 0$ and conditions (3.12) hold. As a proper example we formulate the remark below.

Remark 3.6 *If*

$$\alpha b < \beta, \quad \text{and} \quad 1 < \frac{2\gamma}{\beta^2}, \quad (3.19)$$

then for all $a > \frac{1}{2}\beta + \frac{2\gamma}{\beta} - \alpha b$ the steady state of system (3.1) with the shifted Erlang probability densities given by (3.4)–(3.5) with $m_1 = 2$, $m_2 = 1$ loses its stability at $\sigma = \bar{\sigma}$ and the Hopf bifurcation occurs at this point.

Proof : First, note that under the assumptions of the remark if $a \geq \alpha b \min\left\{1, \frac{2\gamma}{\beta^2}\right\}$, then condition (3.11) holds and Theorem 3.5 implies the assertion of the remark. If $a > \frac{1}{2}\beta + \frac{2\gamma}{\beta} - \alpha b$ and conditions (3.12) hold then Theorem 3.5 also implies the assertion of the remark. We show that for some set of parameters these conditions can be fulfilled simultaneously.

Consider $a < \alpha b \min\left\{1, \frac{2\gamma}{\beta^2}\right\}$. The second inequality of (3.19) implies that $\min\left\{1, \frac{2\gamma}{\beta^2}\right\} = 1$. Hence, the stability condition of steady state for $\sigma = 0$ and the first condition (3.12) reads

$$\frac{1}{2}\beta + \frac{2\gamma}{\beta} - \alpha b < a < \alpha b. \quad (3.20)$$

First, we show for some parameters inequalities (3.20) give a non empty set of a . This is true if the following inequalities

$$\frac{1}{2}\beta + \frac{2\gamma}{\beta} < 2\alpha b < 2\beta \quad (3.21)$$

hold, where the second inequality in (3.21) is just the first one in (3.19). Inequalities (3.21) do not contradict each other if and only if

$$\frac{1}{2}\beta + \frac{2\gamma}{\beta} < 2\beta. \quad (3.22)$$

Thus, if $\frac{2\gamma}{\beta^2} < 3/2$, then there is a non-empty set of αb such that inequalities (3.21) hold and for such αb (3.20) determines a non-empty set of a .

Now, we show that if (3.19) and the first inequality of (3.12) hold then the second inequality of (3.12) also holds.

Note that the assumption $\alpha b < \beta$ means that the right hand side of the second inequality of (3.12) is a decreasing function of a (of course we need to use here the first inequality of (3.12) that guarantees the positivity of the expression under the second power), while the left hand-side is an increasing function of a . Since our assumptions imply that $a < \alpha b$, it is enough to check if inequality (3.12) holds for $a = \alpha b$.

Rearranging terms we obtain

$$27\alpha^6 b^6 < 27(\alpha^3 b^3 + \alpha b(2\gamma - \beta^2))^2.$$

The above inequality obviously holds as $2\gamma > \beta^2$, which completes the proof. ■

For the general case of system (3.1) with the shifted Erlang probability densities given by (3.4)–(3.5) the characteristic function $D(\lambda)$ is given by (3.13) and the auxiliary function F is given by (3.14). It is easy to see that the highest power of ω is $4 + 2m_M$ and the coefficient of it is 1. Moreover, we have $F(0) < 0$. Thus, there exists $\omega_0 > 0$ such that $F(\omega_0) = 0$ and the roots cross the imaginary axis from the left to the right half-plane. Thus, using Theorem 1 from [45], we can deduce the following

Remark 3.7 *If all roots of $F(\omega)$ given by (3.14) are simple, and the trivial steady state of system (3.1) with the shifted Erlang probability densities given by (3.4)–(3.5) is locally asymptotically stable for $\sigma = 0$, then it loses its stability due to the Hopf bifurcation for some $\sigma_0 > 0$ and it is unstable for $\sigma > \sigma_0$ with some $\sigma_\infty \geq \sigma_0$.*

It seems that the case of multiple roots of $F(\omega)$ is non-generic, however we will not prove it here.

3.2.2 Piecewise linear probability densities

For the function defined by (3.3) we have

$$\int_0^\infty f_i(\tau) e^{-\lambda\tau} d\tau = \frac{e^{-\lambda\sigma}}{\lambda^2 \varepsilon^2} (e^{\lambda\varepsilon} + e^{-\lambda\varepsilon} - 2) = \frac{2e^{-\lambda\sigma}}{\lambda^2 \varepsilon^2} (\cosh(\lambda\varepsilon) - 1)$$

and thus the characteristic function for the trivial steady state of system (3.1) reads

$$W(\lambda) = \lambda^2 + \lambda \int_0^\infty (rf_1(\tau) + \alpha b f_2(\tau)) e^{-\lambda\tau} d\tau + \gamma \int_0^\infty f_1(\tau) e^{-\lambda\tau} d\tau,$$

which is equivalent to

$$W(\lambda) = \lambda^2 + (\lambda r + \gamma) \frac{2e^{-\lambda\sigma}}{\lambda^2 \varepsilon^2} (\cosh(\lambda\varepsilon) - 1) + \lambda \alpha b \frac{2e^{-\lambda\sigma}}{\lambda^2 \varepsilon^2} (\cosh(\lambda\varepsilon) - 1). \quad (3.23)$$

Finding zeros of function (3.23) is not a trivial task. If the characteristic function has the form $W(\lambda) = P(\lambda) + Q(\lambda) e^{-\lambda\tau}$, where P and Q are polynomials, one could use the Mikhailov Criterion [46], to estimate the number of zeros of the characteristic function lying in the right half of complex plane. However, in the considered case we do not have strict polynomials. Therefore, we use a generalised

Mikhailov Criterion (for details see A). Clearly, $\cosh(z) = \sum_{n=0}^{\infty} \frac{z^{2n}}{(2n)!}$, for $z \in \mathbb{C}$ is an analytic function, hence $\frac{\cosh(z)-1}{z^2}$ is also analytic. Consequently, the function W defined by (3.23) is also analytical. Moreover, obviously condition (A.1) holds. Thus, we can apply the generalized Mikhailov Criterion.

Considering $\sigma \geq \varepsilon > 0$, we have

$$W(\lambda) = \lambda^2 + (\lambda\beta + \gamma)g(\lambda\varepsilon)e^{-\lambda\sigma}, \quad (3.24)$$

where

$$g(x) = \frac{2(\cosh x - 1)}{x^2}, \quad g_1(x) = g(ix) = \frac{2 - 2\cos x}{x^2}. \quad (3.25)$$

Thus,

$$\operatorname{Re}(W(i\omega)) = -\omega^2 + g_1(\omega\varepsilon)(\gamma \cos(\omega\sigma) + \beta\omega \sin(\omega\sigma)), \quad (3.26)$$

$$\operatorname{Im}(W(i\omega)) = g_1(\omega\varepsilon)(\beta\omega \cos(\omega\sigma) - \gamma \sin(\omega\sigma)). \quad (3.27)$$

Here we formulate sufficient condition for stability of the trivial steady state of system (3.1) for the piecewise linear distributions defined by (3.3) with $\sigma \geq \varepsilon > 0$. This condition is clearly not necessary, what we will show numerically in the next section.

Proposition 3.8 *Let $b > \mu$, β and γ be defined by (3.7). Then for*

(i)

$$\sigma < \frac{\pi}{\beta + \sqrt{\beta^2 + 4\gamma} + \frac{\gamma}{\beta}\pi} \quad (3.28)$$

the trivial steady state of system (3.1) with the piecewise linear distributions defined by (3.3) and $\sigma \geq \varepsilon > 0$ is locally asymptotically stable.

(ii)

$$\frac{\beta}{\gamma} < \sigma < \frac{2\pi}{\beta + \sqrt{\beta^2 + 4\gamma}} \quad (3.29)$$

the trivial steady state of system (3.1) with the piecewise linear distributions defined by (3.3) with $\sigma \geq \varepsilon > 0$ is unstable.

Proof : We use the generalized Mikhailov Criterion (for details see A) to show that the change of the argument of $W(i\omega)$ as ω varies from 0 to ∞ is equal to π . In fact, we show that the behaviour of the hodograph is more restrictive, namely that for some $\bar{\omega} > 0$ we have $\operatorname{Re}(W(i\omega)) < 0$ for $\omega > \bar{\omega}$, while $\operatorname{Im}(W(i\omega)) > 0$ for $\omega \in [0, \bar{\omega}]$. To this end first, note that if $g_1(\omega\varepsilon) = 0$ and $\omega > 0$, then $\operatorname{Re}(W(i\omega)) < 0$. Thus, without loss of generality we assume that $g_1(\omega\varepsilon) > 0$.

First, let us estimate the real part of $W(i\omega)$ given by (3.26). Since $b > \mu$ and $g_1(\varepsilon\omega) \leq 1$ we have

$$\operatorname{Re}(W(i\omega)) \leq -\omega^2 + \gamma + \omega\beta =: g_R(\omega).$$

Now, let us consider the imaginary part of $W(i\omega)$. In fact, since we are interested in the sign of it and $g_1(\varepsilon\omega) \geq 0$ it is enough to consider the sign of

$$\omega\beta \cos(\omega\sigma) - \gamma \sin(\omega\sigma) = g_I(\omega\sigma),$$

where

$$g_I(x) = \frac{\beta}{\sigma} x \cos x - \gamma \sin x.$$

Note, that (3.28) implies $\beta > \gamma\sigma$, and thus $g_I(x) > 0$ for x close to 0. On the other hand, $g_I(\pi/2) = -\gamma < 0$. It is also easy to check, that $g_I(x)$ has a unique zero in $(0, \pi/2)$ for $\beta > \gamma\sigma$. Below, we give some estimation for this zero.

Since $\tan x < \frac{\pi}{2} \frac{x}{\frac{\pi}{2} - x}$, for $x \in (0, \pi/2)$ we have

$$\frac{\beta}{\gamma\sigma}x \geq \frac{\pi}{2} \frac{x}{\frac{\pi}{2} - x} > \tan x. \quad (3.30)$$

A simple algebraic yields that the first inequality of (3.30) is fulfilled for all

$$0 < x \leq \frac{\pi}{2} \left(1 - \sigma \cdot \frac{\gamma}{\beta} \right) < \frac{\pi}{2}.$$

Thus, as long as $\omega\sigma \leq \frac{\pi}{2} \left(1 - \sigma \cdot \frac{\gamma}{\beta} \right)$ we have $\text{Im}(W(i\omega)) > 0$.

However, g_R is a quadratic polynomial with $g_R(0) > 0$. Moreover, the coefficient of ω^2 is negative and the positive root of g_R is equal to $\frac{1}{2}(\beta + \sqrt{\beta^2 + 4\gamma})$. An easy algebraic manipulation shows that condition (3.28) is equivalent to

$$\frac{\sigma}{2}(\beta + \sqrt{\beta^2 + 4\gamma}) < \frac{\pi}{2} \left(1 - \sigma \cdot \frac{\gamma}{\beta} \right)$$

and thus $g_R(\omega) < 0$ for all $\sigma\omega > \frac{\pi}{2} \left(1 - \sigma \cdot \frac{\gamma}{\beta} \right)$, which completes the proof of part (i).

The idea of the proof of part (ii) is similar to the proof of part (i). However, this time we want to show that for $\sigma\omega \in (0, \pi)$ the imaginary part $\text{Im}(W(i\omega)) < 0$, while for $\sigma\omega > \pi$ the real part $\text{Re}(W(i\omega)) < 0$. This indicates that the hodograph goes below the $(0, 0)$ point on the complex plane when ω tends to $+\infty$ and hence the change of the argument of $W(i\omega)$ differs from π . Hence, from the generalized Mikhialov Criterion it is clear that the trivial steady state of system (3.1) is unstable.

Note, that for $\omega\sigma \in (\pi/2, \pi)$ we have $\text{Re}(W(i\omega)) < 0$ due to the fact that on this interval cosine is negative and sine is positive. Consider $\omega\sigma \in (0, \pi/2)$. Thus, cosine is positive and inequality $\beta\omega \cos(\omega\sigma) - \gamma \sin(\omega\sigma) < 0$ is equivalent to

$$\frac{\beta}{\sigma\gamma}\omega\sigma < \tan(\omega\sigma). \quad (3.31)$$

The right hand side of (3.31) is a strictly increasing convex function on $(0, \pi/2)$ and have the first derivative at 0 equal to 1. Thus, the first inequality of (3.29) implies (3.31).

Now, it is enough to show that $g_R(\pi/\sigma) < 0$. A straightforth calculation yields

$$-\left(\frac{\pi}{\sigma}\right)^2 + \beta\frac{\pi}{\sigma} + \gamma < 0.$$

Solving quadratic equation we get

$$\sigma < \frac{2\pi}{\beta + \sqrt{\beta^2 + 4\gamma}},$$

which is the second inequality of (3.29). ■

Remark 3.9 Note, that (3.28) implies $\sigma < \beta/\gamma$ and consequently, conditions (3.29) and (3.28) are mutually exclusive.

Theorem 3.10 If the trivial steady state of system (3.1) with the piecewise linear distributions defined by (3.3) and $\sigma \geq \varepsilon > 0$ is locally asymptotically stable for $\sigma = \varepsilon$ and the function

$$F(\omega) = \omega^4 - \varepsilon^2(\omega^2\beta^2 + \gamma^2)g_1^2(\varepsilon\omega),$$

where g_1 is defined by (3.25) has no multiple positive zeros, then the steady state is locally asymptotically stable for some $\sigma \in [\varepsilon, \sigma_0)$ and it is unstable for $\sigma > \bar{\sigma}$, with $\sigma_0 \leq \bar{\sigma}$. At $\sigma = \sigma_0$ the Hopf bifurcation occurs.

Proof : For the considered case the characteristic function is given by (3.24). It can be easily seen that if $W(i\omega) = 0$, then

$$\| -i\omega \|^2 = \varepsilon^2 \| i\omega\beta + \gamma \|^2 \| g(i\omega\varepsilon) \|^2,$$

and thus

$$\omega^4 = \varepsilon^2 (\omega^2 \beta^2 + \gamma^2) g_1^2(\varepsilon\omega),$$

where g_1 is defined by (3.25). The function F has the following properties

$$F(0) = -\varepsilon^2 \gamma^2 < 0, \quad \text{and} \quad \lim_{\omega \rightarrow +\infty} F(\omega) = +\infty.$$

Hence, we conclude that there exists $\omega_0 > 0$ such that $F(\omega_0) = 0$ and $F'(\omega_0) \geq 0$. It is assumed that all zeros of $F(\omega)$ are simple, thus $F'(\omega_0) > 0$ and by Theorem 1 from [45], the thesis of theorem is proved. ■

Remark 3.11 *Note, that the case where the function F has multiple positive zeros is not generic.*

Proof : Consider the case of the multiple positive zero(s) of F . First, note the following facts:

- (a) F is a analytic function so it has isolated zeros;
- (b) For $\omega > \max\{\varepsilon \sqrt{\beta^2 + \gamma^2}, 1\}$ inequality $F(\omega) > 0$ holds.
- (c) If $g_1(\varepsilon\omega) = 0$, then $F(\omega) = (2k\pi/\varepsilon)^4 > 0$ for some $k \in \mathbb{N}$, $k \geq 1$.

Facts (a) and (b) imply, that F has a finite number of zeros. Suppose that for the arbitrary values of β_0 and γ_0 the function F has the multiple zero at $\omega_{m,j}$, for some $j = 1, 2, \dots, j_M$, where $j_M \geq 1$ is a natural number. Now, consider the interval $I = [0, \max\{\varepsilon \sqrt{\beta^2 + \gamma^2}, 1\} + 1]$. Clearly, $\partial F / \partial \gamma < 0$ holds for all $\omega \neq 2k\pi/\varepsilon$. Moreover, F' is also an analytic function so it has a finite number of zeros in the interval I . Thus, we choose $0 < \epsilon_\gamma < 1$ so small that for all $\gamma \in (\gamma_0 - \epsilon_\gamma, \gamma_0 + \epsilon_\gamma) \setminus \{\gamma_0\}$ the function F has no multiple root in the interval I . This completes the proof. ■

4 Stability results for parameters estimated by Hahnfeldt *et al.*

In the previous section, we analytically investigated the stability of the trivial steady state of the family of angiogenesis models with distributed delays (3.1) and distributions characterized by the probability densities f_i given by (3.3) and (3.4)–(3.5). System (3.1) is a rescaled version of (2.1), where the trivial steady state of (3.1) corresponds to the positive steady state of (2.1).

In this section we illustrate our outcome for particular model parameters considered earlier in the literature, that is the parameters estimated by Hahnfeldt *et al.* in the case of the model without the treatment (see [47]). Namely, we consider the following set of parameters:

$$\mu = 0, \quad a_H = 8.73 \times 10^{-3}, \quad b = 5.85, \quad r = 0.192, \quad (4.1)$$

and we take the function $h(\theta) = -\ln \theta$. We present stability results for the distributed models for two different values of parameter α . To keep the description short, for model (3.1) with $\alpha = 1$ we would refer to as the Hahnfeldt *et al.* model, while to model (3.1) with $\alpha = 0$ as the d'Onofrio-Gandolfi model. However, in this paper we also consider positive values of μ that can be interpreted as a constant anti-angiogenic treatment.

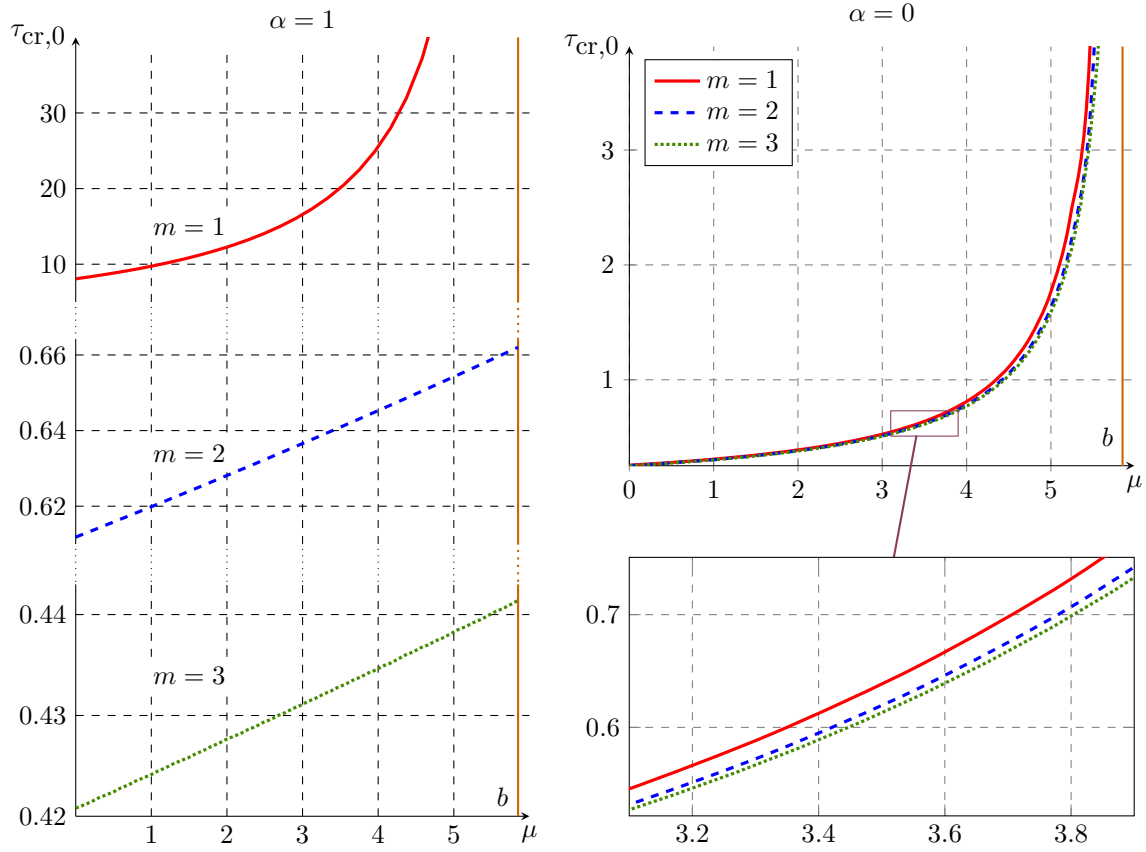


Figure 1: Dependence of the critical average delay value in the case of the non-shifted Erlang distributions given by (3.4)–(3.5) with $m_1 = m_2 = m$ on the constant treatment coefficient μ for system (3.1). The critical average delay is defined by $\tau_{cr,0} = m/a_{cr,0}$, where $a_{cr,0}$ is the critical value of parameter a for which stability change occurs (see Proposition 3.3). In the left-hand side panel results for the Hahnfeldt *et al.* model ($\alpha = 1$) are shown while in the right-hand side panel results for the d’Onofrio-Gandolfi model ($\alpha = 0$). All other parameters, except μ , are defined by (4.1).

4.1 Erlang probability densities

First, focus on model (3.1) with the non-shifted Erlang distributions given by (3.4)–(3.5) with $\sigma = 0$, $i = 1, 2$. The expression m/a describes the average delay. On the other hand, in the more general case of $m_1 \neq m_2$ a similar interpretation leads to the conclusion that the average delays are m_1/a and m_2/a . One could also consider the arbitrary values $a = a_1$ for f_1 and $a = a_2$ for f_2 , but then the analytical expressions become very complicated and we decided not to study these cases here.

In Fig. 1 the dependence of the critical average delay value $\tau_{cr,0}$ with $m_i = m$ ($i = 1, 2$) on the constant treatment coefficient μ is presented. In the case of the non-shifted Erlang distributions the average delay is defined by $\tau_{cr,0} = m/a_{cr,0}$ and the left-hand side panel and the right-hand side panel present results for the Hahnfeldt *et al.* model ($\alpha = 1$) and the d’Onofrio-Gandolfi model ($\alpha = 0$), respectively. The curves were calculated from the stability conditions given in Proposition 3.3. The stability regions of the trivial steady state of (3.1) with the non-shifted Erlang distributions are below curves, while above them there are the instability regions. It is worth to emphasise that there is a qualitative difference between the cases: $m = 1$ and $m = 2, 3$ for the Hahnfeldt *et al.* model, while there is no such a difference for the d’Onofrio-Gandolfi model. Clearly, for the Hahnfeldt *et al.* model and $m = 1$ the critical average delay $\tau_{cr,0}$ tends to $+\infty$ as $\mu \rightarrow b$ while for $m = 2$ and $m = 3$ we have $\tau_{cr,0}|_{\mu=b} = 4/\beta \approx 0.662$ and $\tau_{cr,0}|_{\mu=b} = 8/(3\beta) \approx 0.441$, respectively. Nevertheless, for the d’Onofrio-Gandolfi model the critical average value of delays are almost the same for the case $m = 1, 2$ and $m = 3$ for $\mu \in [0, b)$ and the behaviour is qualitatively comparable with the result for the

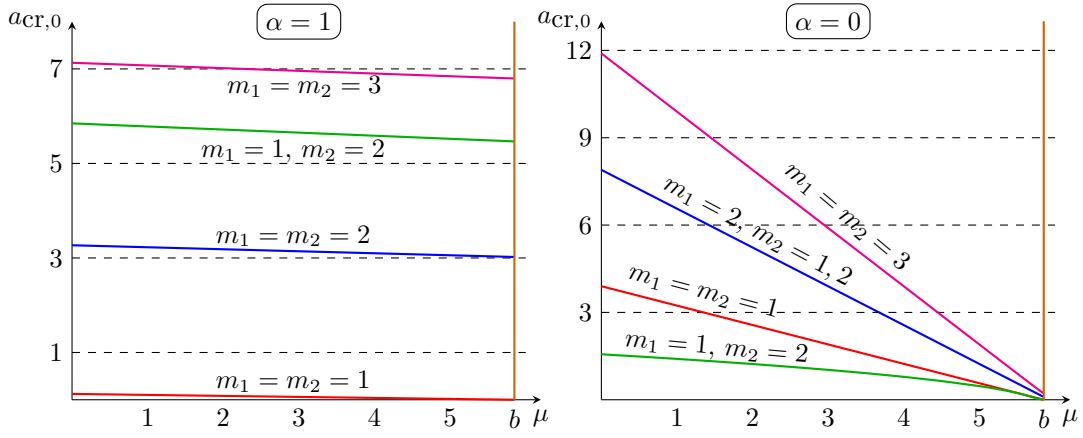


Figure 2: Dependence of the critical value of parameter a for the trivial steady state of system (3.1) with the non-shifted Erlang probability densities given by (3.4)–(3.5) (i.e. $\sigma = 0$). The regions above the plotted curves corresponds to the stability regions for the particular choices of parameters m_i , $i = 1, 2$. For $m_1 = 2, m_2 = 1$ and $\alpha = 1$ the trivial steady state is always stable. All other parameters, except μ , are defined by (4.1).

Hahnfeldt *et al.* model for $m = 1$. Moreover, in the considered cases the critical average delay values in the case of the non-shifted Erlang distributions are the increasing functions of μ . This means that the increase of treatment increases the stability region.

In Fig. 2 we plot the critical value of parameter a , that is $a_{cr,0}$, for the trivial steady state of system (3.1) with the non-shifted Erlang probability densities given by (3.4)–(3.5) (i.e. $\sigma = 0$) calculated based on Proposition 3.3. Here, the regions above the plotted curves correspond to the stability regions for the particular choices of parameters m_i , $i = 1, 2$, while those below correspond to the instability regions. It should be clarified that for the case $\alpha = 1, m_1 = 2$ and $m_2 = 1$ the steady state is stable for all values of a . We see that all plotted functions are decreasing as functions of the strength of constant treatment μ . However, already for the non-shifted Erlang probability densities we observe a large differences between both models regarding the model dynamics. For the Hahnfeldt *et al.* model we have the largest stability region for $m_1 = 2$ and $m_2 = 1$, while in the case of the d’Onofrio-Gandolfi model for $m_1 = 1$ and $m_2 = 2$. Moreover, for the case $m_1 = 2$ and $m_2 = 1$ the steady state is stable independently of the parameter a for the Hahnfeldt *et al.* model, while in the same case of m_i for the d’Onofrio-Gandolfi model the steady state might change its stability with the change of a . Additionally, for $\alpha = 0$ the sizes of the stability regions for $m_i = 2$ and $m_1 = 2, m_2 = 1$ are the same and it is not the case $\alpha = 1$.

The stability of the steady state for the non-shifted Erlang distributions can be determined by the Routh-Hurwitz criterion, although it may require tedious calculations, in particular for large values of parameters m_1 and/or m_2 . On the other hand, the analytical results we obtained for the shifted Erlang distributions are rather limited. The results presented in Theorem 3.5 are only the existence results and give no information of the magnitude of the critical value of σ for which stability is lost. Although, it is possible to derive an expression for the critical value of σ , it would involve arccos of some algebraic function of ω_0 , which value cannot be, in general, determined analytically and the final result would not be informative. In consequence, we decided to calculate numerically the critical values of the average delay $\tau_{cr,\sigma}$ for the considered model with the shifted Erlang distributions for parameters given by (4.1). Clearly, if one wish to calculate the critical average delay for model with the shifted Erlang distributions it appears that it depends on sigma directly and is given by $\tau_{cr,\sigma} = m/a + \sigma_{cr}$, where σ_{cr} is a critical value of σ defined in Theorem 3.5. In Fig. 3 we present the stability results for the trivial steady state of system (3.1) with the shifted Erlang probability densities given by (3.4)–(3.5). In particular, in Fig. 3 (left column) we plot the dependence of $\tau_{cr,\sigma}$ on the treatment strength μ for the particular choices of parameters m_i and the particular choices of parameter a for the model with

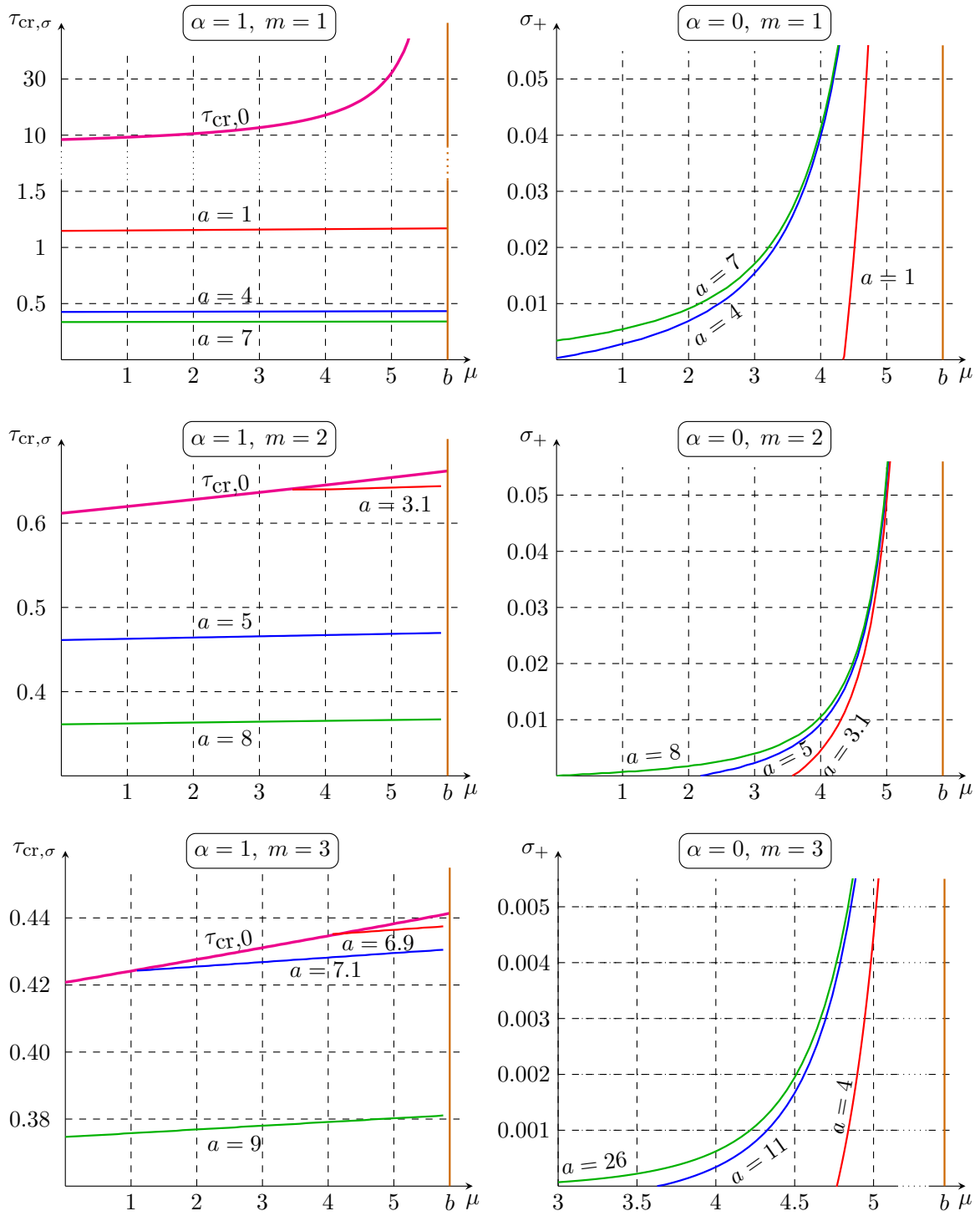


Figure 3: Dependence of the critical average delay $\tau_{cr,\sigma}$ for the trivial steady state of system (3.1) with shifted Erlang probability densities given by (3.4)–(3.5) for the particular choice of parameter a and comparison with the critical value of the average delay $\tau_{cr,0}$ in the case of $\sigma = 0$. For the case of the Hahnfeldt *et al.* model (i.e. $\alpha = 1$), presented in the left column, the regions above the plotted curves correspond to the instability regions for the particular choices of parameters $m_1 = m_2$ and of parameter a . The stability region is the region below curves. For the d'Onofrio-Gandolfi model (i.e. $\alpha = 0$) presented in the right column, the difference between critical value of the average delay $\tau_{cr,0}$ in the case of $\sigma = 0$ and the critical average delays $\tau_{cr,\sigma}$ for chosen values of a are so small that the plot would be non-informative. Thus, in the right column we presented the difference $\sigma_+ = \tau_{cr,0} - \tau_{cr,\sigma}$. All other parameters, except μ , are defined by (4.1).

$\alpha = 1$. Similarly as in Fig. 1 the regions below the plotted curves correspond to the stability regions. Additionally, we plot $\tau_{cr,0}(\mu)$ curves to indicate thresholds for which the destabilizations occur in the case $\sigma = 0$. If the curve for a considered a is above the $\tau_{cr,0}$ curve, then the steady state is unstable for $\sigma = 0$ and remains unstable for all $\sigma > 0$. In the both cases $m_i = 1$ and $m_i = 2$ the increase of the value of the parameter a (which is equivalent to decrease of the critical average delay), defining the shape of the probability densities, implies the decrease of the stability regions of the steady state. Since the corresponding curves for $\alpha = 0$ are very close to each other instead of plotting them directly we decided to plot the differences $\sigma_+ = \tau_{cr,0} - \tau_{cr,\sigma}$ between the critical values of the average delays $\tau_{cr,0}$ in the case $\sigma = 0$ and the critical average delays $\tau_{cr,\sigma}$ for the chosen values of a . Clearly, whenever plotted curve reaches the μ axis the trivial steady state becomes unstable for all $\sigma \geq 0$. From Fig. 3 (right column) we deduce that the stability areas again decrease with the increase of the parameter a .

4.2 Piecewise linear distributions

Let us focus on the stability and instability regions of the trivial steady state of system (3.1) with piecewise linear distributions defined by (3.3). Since in such a case we have smaller number of parameters defining the shape of the probability density we are able to plot the stability regions in (σ, ε) plane, see Fig. 4. Note that, for $\varepsilon > \sigma$ system (3.1) becomes a neutral system, which is out of our consideration hence this region is greyed. Clearly, the estimations obtained in Proposition 3.8 are rough. However, solving numerically a system $\text{Re}W(i\omega) = 0$, $\text{Im}W(i\omega) = 0$, where real and imaginary part of characteristic function are given by (3.26) and (3.27), respectively, we are able to calculate the stability region and the curve for which the stability change occurs. This line was plotted in Fig. 4 as a thick solid blue line.

Additionally, we plot (in both panels) the vertical dashed lines that denote the conditions guaranteeing stability (see Proposition 3.8(i)) or instability (see Proposition 3.8(ii)) of the trivial steady state. For the Hahnfeldt *et al.* model (left panel in Fig. 4) the condition (3.28) from Proposition 3.8 is denoted by a vertical dashed line. In that case, the condition (3.29) cannot be fulfilled since the expression on the right-hand side of (3.29) is always smaller than β/γ . For the d'Onofrio-Gandolfi model the dashed vertical line on the left to the solid vertical line indicates the condition (3.28). Two dashed vertical lines on the right to the solid one indicate the region in which the condition (3.29) is fulfilled. Those numerical results show that the conditions from Proposition 3.8 are only sufficient but not necessary. From the figure we also deduce that the stability region for the trivial steady state for the d'Onofrio-Gandolfi model is smaller than the one for the distributed Hahnfeldt *et al.* model. Moreover, computed by us the critical values of σ for $\varepsilon \rightarrow 0$ and both $\alpha = 1$ and $\alpha = 0$ agrees with those calculated by Piotrowska and Forys in [33] for the models with discrete equal delays. That agrees with the intuition, since for $\varepsilon \rightarrow 0$ models given by (3.1) with piecewise linear distributions defined by (3.3) reduce to the models with double discrete delay.

For $\mu > 0$ and the Hahnfeldt *et al.* model we observe a move of the stability switch curve to the right with hardly any change in the shape indicating that the stability region increases with increase of parameter μ , see left panel in Fig. 5. This shift is very small. Moreover, for $\mu = b$ we obtain limiting values: 0.26 for $\varepsilon \rightarrow 0$ and 0.33 for $\varepsilon \rightarrow \sigma$. On the other hand, for the d'Onofrio-Gandolfi model the change is more visible. The lines start to lean to the right. For small μ , the change is quite small, compare with right panel in Fig. 4. For example, for $\mu = 3$ we obtain $\sigma = 0.509$ for $\varepsilon \rightarrow 0$ and $\sigma = 0.59$ for $\varepsilon = \sigma$. As μ approaches to b the changes become more rapid. For $\mu = 5.7$ we have $\sigma = 5.326$ for $\varepsilon \rightarrow 0$ and $\sigma = 5.632$ for $\varepsilon = \sigma$, while for $\mu = b$ we have $\sigma = 8.181$ and $\sigma = 10.065$ for $\varepsilon \rightarrow 0$ and $\varepsilon = \sigma$, respectively.

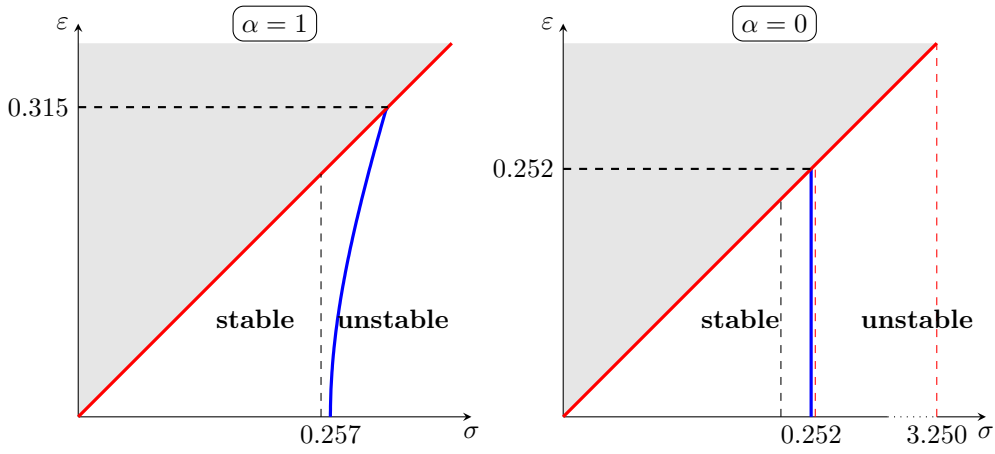


Figure 4: Stability and instability of the trivial steady state of system (3.1) with piecewise linear distributions defined by (3.3) with $\sigma > 0$, $\varepsilon > 0$, $i = 1, 2$ for the parameters given by (4.1) with $\alpha = 1$ (the left hand-side panel) and $\alpha = 0$ (the right-hand side panel). The greyed part denotes the region where $\varepsilon > \sigma$ for which system (3.1) becomes a neutral system. The solid lines indicate the stability switch. In the left-hand side panel, the vertical dashed line denotes the condition (3.28) from Proposition 3.8. In the right-hand side panel, the vertical dash line in the stability region denotes the scope of the condition (3.28) form Proposition 3.8, while two vertical dash lines in the instability region denote the scope of condition (3.29).

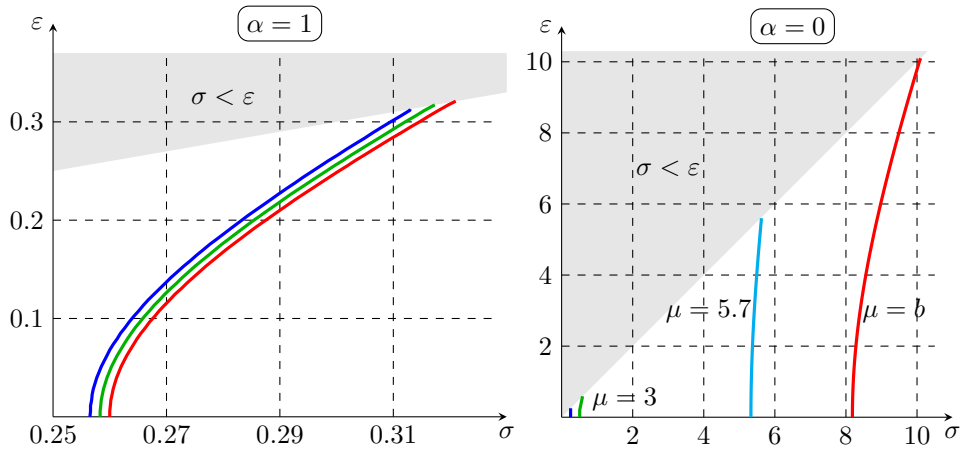


Figure 5: Stability and instability of the trivial steady state of system (3.1) with piecewise linear distributions defined by (3.3) with $\sigma > 0$, $\varepsilon > 0$, $i = 1, 2$ for the parameters given by (4.1) with $\alpha = 1$ (the left hand-side panel) and $\alpha = 0$ (the right-hand side panel) and different μ . The greyed part denotes the region where $\varepsilon > \sigma$ for which system (3.1) becomes a neutral system. The solid lines indicate the stability switch for (from left to right) $\mu = 0, 3, b$ for $\alpha = 1$ and for $\mu = 0, 3, 5.7, b$ for $\alpha = 0$.

5 Discussion

Although discrete delays often appear in models describing various biological phenomena, e.g. [48–58] and references therein, it is obvious that in natural processes delay, if it exists, is usually somehow distributed around some average value due to differences between individuals and/or environmental noise. Thus, we believe that distributed delays are more realistic. However, in some cases, when the distribution has small variance and compact support discrete delays may be treated as a good approximation. Clearly, models with discrete and distributed delays might have different dynamics in some ranges of parameters. In the presented paper we have compared the behaviour of two types of

systems in the context of the stability of the steady state for a particular family of models describing the tumour angiogenesis process.

Table 1: The critical average delay value $\tau_{cr,0}$ in the case of non-shifted Erlang distributions given by (3.4)–(3.5) with $m_1 = m_2 = m$ and $a_1 = a_2 = a$ for arbitrary chosen parameters μ for system (3.1). The critical average delay is defined by $\tau_{cr,0} = m/a_{cr,0}$, where $a_{cr,0}$ is the critical value of parameter a for which the stability change occurs (see Theorem 3.3).

μ	Hahnfeldt <i>et al.</i> model ($\alpha = 1$)				d’Onofrio-Gandolfi model ($\alpha = 0$)			
	0	2	4	5.85	0	2	4	5.85
$m_1 = m_2 = 1$	8.069	12.261	25.515	∞	0.256	0.390	0.811	∞
$m_1 = m_2 = 2$	0.611	0.628	0.645	0.662	0.253	0.382	0.780	20.833
$m_1 = m_2 = 3$	0.421	0.428	0.435	0.441	0.252	0.380	0.770	13.889

Presented analysis of distributed models includes: the uniqueness, the positivity and the global existence of the solutions, the existence of the steady state and the possibility of the existence of the stability switches. We have analytically derived conditions, involving the parameters defining the probability densities, guaranteeing the stability or instability of the steady state. We have also shown that in some cases the single stability switch is observed and the Hopf bifurcation occurs.

For the particular set of parameters, estimated by Hahnfeldt *et al.*, we have investigated the stability regions for steady state. We compared the results for both the Hahnfeldt *et al.* ($\alpha = 1$) and the d’Onofrio-Gandolfi ($\alpha = 0$) models in the case of different probability densities. For both models we considered the Erlang shifted and non-shifted distributions as well as the piecewise linear distributions. We want to emphasise here that, in the general case, it is hard to say for which model Hahnfeldt *et al.* or d’Onofrio-Gandolfi the stability region is larger since it strongly depends on the considered probability densities and their shapes. However, we observe certain similarities.

First, for $\mu = 0$, i.e. the family of models without treatment, we see that for the Hahnfeldt *et al.* model with non-shifted Erlang probability density the larger $m_i = m$ are the smaller the stability region is, see Fig. 1 and Table 1. The same holds for the d’Onofrio-Gandolfi model with the non-shifted Erlang distributions, see Table 1 and moreover, for all considered $m_i = m$, $i = 1, 2$ (and $\mu = 0$) for the Hahnfeldt *et al.* model the stability region is larger than for d’Onofrio-Gandolfi one. Similarly, for the models with the piecewise linear distributions the stability region for $\mu = 0$ for the Hahnfeldt *et al.* model is larger than the one for the d’Onofrio-Gandolfi model, compare Fig. 4.

If we consider a positive parameter μ smaller than b (to ensure the non-negativity of the steady state of model (2.1), which corresponds to the trivial steady state of (3.1)), we observe a similar tendency for the Erlang distributions in dependence on the parameters $m_1 = m_2$ (compare Table 1 for the non-shifted distribution case). However, the dependence on μ depends strongly on the chosen model. For the Hahnfeldt *et al.* model and $m_1 = m_2 \geq 2$, this dependence is almost linear and very weak, while for the d’Onofrio-Gandolfi model it is much stronger. In results, for $m_1 = m_2 \geq 2$ and any sufficiently large value of $\mu \in [0, b)$ the critical average delay for the Hahnfeldt *et al.* model becomes smaller than for the d’Onofrio-Gandolfi model. The case $m_1 = m_2 = 1$ is different. Dependence on μ is similar for both models and the critical average delay for the Hahnfeldt *et al.* model stays larger than for the d’Onofrio-Gandolfi model for any given value of μ . Similarly, for different values of m_i , it seems that dependence on μ is stronger for the d’Onofrio-Gandolfi model, see Fig. 2. Nevertheless, for the d’Onofrio-Gandolfi model with the non-shifted Erlang distributions there is no difference regarding the stability results between cases $m_1 = m_2 = 2$ and $m_1 = 2, m_2 = 1$, which is not the case for the Hahnfeldt *et al.* model, where for $m_1 = 2, m_2 = 1$ we have stability independently on the value of parameter a . For the shifted Erlang distributions we have investigated the changes of the size of the stability region also in the context of the change of the value of parameter a . For both the Hahnfeldt *et al.* and d’Onofrio-Gandolfi models we see that for all considered $m = m_i$, $i = 1, 2$, the increase of the parameter a decrease the stability region, however in the case of d’Onofrio-Gandolfi

model we have compared the differences of the $\tau_{cr,0} - \tau_{cr,\sigma}$. A similar increase of the stability region with a decrease of concentration of delay distribution was observed in [36] for one linear equation with distributed delay and Erlang probability density.

Nevertheless, we see that since for all considered cases of the shifted and non-shifted Erlang distributed models $\tau_{cr,\sigma}$ and $\tau_{cr,0}$, respectively, are increasing (sometimes slightly) functions of variable μ implying that the increase of the constant treatment strength enlarges the stability regions for the positive steady state of model (2.1). Our analysis also shows that the increase of the positive parameter μ enlarges the stability area for the steady state for both (Hahnfeldt *et al.* and d'Onofrio-Gandolfi) distributed models with the piecewise linear distributions, but this time for the d'Onofrio-Gandolfi model this increase is more pronounced than for the distributed Hahnfeldt *et al.* model, see Fig. 5. Moreover, for small values of parameter μ the stability region for the Hahnfeldt *et al.* model with the piecewise linear distributions is larger than the one for the d'Onofrio-Gandolfi model, while for the larger values of μ the situation is opposite. Performed simulations show that the change occurs before $\mu \approx 1.42$.

The variances for the shifted and non-shifted Erlang distributions are given by $\frac{m_i}{a^2}$ and they give a measure of the degree of the concentration of the delay around the mean. Actually, a better measure of the spread of the distribution around the mean for our purposes is the coefficient of variation, i.e. the ratio of the standard deviation to the mean, that is $\sqrt{m_i}/(a\sigma + m_i)$. Clearly, for the non-shifted distributions we have $1/\sqrt{m_i}$, which implies that larger parameter m_i yields smaller the considered ratio. Hence, the increase of m_i decreases the percentage dispersion of the average delay. On the other hand, for the shifted Erlang distributions, the coefficient of variation is a decreasing function of σ . This dependence is obvious since the increase of σ with fixed m_i and a means that the average delay is increased while standard deviation remains constant. The coefficient of variation is also a decreasing function of parameter a . On the other hand, if we fix a and σ , and study the influence of m_i , then the coefficient of variation increases if $m_i < a\sigma$ and decreases otherwise.

For piecewise linear distributions ($\sigma \geq \varepsilon$) we have the average value of f_i (defined by (3.3)) equal to σ and the standard deviation given by $\varepsilon/\sqrt{6}$. Hence, the coefficient of variation equals to $\varepsilon/(\sigma\sqrt{6})$. Thus, it is an increasing function of ε (for fixed σ) and a decreasing function of σ (for fixed ε). Thus, we conclude that the percentage dispersion of the average delay is the increasing function of ε and decreasing function of σ and it is always smaller than 1. Clearly, all that should be taken into account whenever the probability distributions describing the characteristics of delays are estimated.

We believe that with the proposed type of models one can describe in a more realistic way the process of angiogenesis. However, the considered model should be validated with the experimental data. Our results show that a system behaviour in the case of distributed delays might be different from the behaviour of the system for discrete delays. Hence, to validate the model with the experimental data it is important to choose the right type of the delay(s) in the model preferably based on the experimental data or hypothesis postulated by the experimentalists. Our study also shows that a shape of probability density for the distributed delays has an essential influence on the model dynamics. On the other hand, it is not a trivial task to choose the right distribution if one has not sufficiently large set of the experimental data and does not assume any particular shape of the distribution. This problem need to be individually addressed according the available data and it should be done for the considered model in the future. In our opinion, models with distributed delays could be also studied in the context of efficiency of different types of tumour therapies.

We would like to emphasise that oscillations in the experimental data for different human and animal cell lines in the context of neoplastic diseases, even without administration of any treatment, has been already widely observed for leukaemia ([59, 60]), B-cell lymphoma ([61]) and solid tumours ([62, 63]). To investigate the origin of such phenomenon a number of mathematical and numerical models has been developed. For example Kuznetsov *et al.*, [64], studying the interactions between an immune system and a tumour by system of ODEs, pointed out that different local and global bifurcations (observed for the realistic parameter values they estimated) showed that there might be

a connection between the phenomena of immunostimulation of tumour growth, formation of “dormant” state and “sneaking through” of tumour. Similarly, Kirschner and Panetta in [65] discussed inter alia the biological implications of the Hopf bifurcation in the case of the tumour-immune system interactions. More recently, Pujo-Menjouet et al. [66], using the model with discrete delay for which the Hopf bifurcation is observed, explained why and how short cell cycle durations gave rise to long period oscillations of order from 40 to 80 day for periodic chronic myelogenous leukaemia patients. At the same time in [67] the bifurcation phenomenon and its role for a white-blood-cell production model with discrete delay was studied. The experimentally observed oscillations in the tumour volume [62, 63] can be explained by the analytic results from earlier and more theoretical paper [68] focussing on the growth of avascular multicellular tumour spheroids, where the delay in the process of proliferation was considered. Later on, this work was extended in [69], while the model with the delay only in the apoptosis process was considered in [70]. Next, the model that took into account delays in both processes was studied in [71]. It is believed that the p53 protein plays an essential role in preventing certain types of cancers and is called “guardian of the genome” [72], hence we could also mention here the models of Hes1 and p53 gene expressions, both with negative feedback, and with discrete time delays proposed by Monk [51]. The model of the Hes1 protein was examined later by Bernard et al. [73] and Bodnar and Bartłomiejczyk [50]. In that cases the mathematical analysis showed, that experimentally observed oscillation can be explained by the time lag present in the system due to the DNA transcription process as well as the diffusion time of mRNA and the Hes1 proteins.

Finally, we discuss shortly possible generalisation of the results obtained in this paper. The first equation of the considered model is quite general and can describe a process with saturation. On the other hand, the second equation comes from a quasi-stationary approximation of some reaction-diffusion equations under particular assumptions that are justified for the angiogenesis process. Thus, most probably it cannot be straightforwardly transformed to describe other biological or medical processes. However, the stability analysis performed in the paper is based on the local properties of the functions. Thus, we may assume a more general form of the second equation namely $q(t)G(p_t/q_t, p)$ (where p_t and q_t according to a functional notation typical for DDEs denote terms with delay) assuming that G is an increasing function in the first variable and decreasing in the second one. Then, in our opinion, under some additional assumptions, one should obtain results similar to those presented in the paper.

A Generalized Mikhailov Criterion

Here we formulate a generalized version of the Mikhailov Criterion (see eg. [46]). The classical formulation of the Mikhailov Criterion is for the characteristic functions that are sums of polynomials multiplied by an exponential function. However, it can be generalized for wider class of functions. Below, we present a detailed formulation.

Theorem A.1 (Generalised Mikhailov Criterion) *Let us assume that $W : \mathbb{C} \rightarrow \mathbb{C}$ is an analytic function, has no zeros on imaginary axis and fulfils*

$$W(\lambda) = \lambda^n + o(\lambda^n), \quad W'(\lambda) = n\lambda^{n-1} + o(\lambda^{n-1}), \quad (\text{A.1})$$

for some natural number n . Then the number of zeros of W in the right-hand complex half-plane is equal to $n/2 - \Delta/\pi$ where

$$\Delta = \Delta_{\omega \in [0, +\infty)} \arg W(i\omega).$$

Note, that Δ denotes the change of argument of the vector $W(i\omega)$ in the positive direction of complex plane as ω increases from 0 to $+\infty$.

Proof : The proof is exactly the same as the proof of the Mikhailov Criterion in [46, Th. 1]. It is based on integration of the characteristic function on the following contour: part of imaginary axis, portion of the imaginary axis from $i\rho$ to $-i\rho$ and a semi-circle of radius ρ with the middle in zero located in the right half of complex plane. The fact that W is an analytic function implies that it has the isolated zeros and all integration can be done in the same way as in [46]. Moreover, the assumption (A.1) implies that all limits calculated in [46] remain the same. ■

B Acknowledgements

The work on this paper was supported by the Polish Ministry of Science and Higher Education, within the Iuventus Plus Grant: "Mathematical modelling of neoplastic processes" grant No. IP2011 041971.

We thank the reviewers for their valuable comments that improved our paper.

References

- [1] J. Folkman, Tumor angiogenesis: therapeutic implications, *N. Engl. J. Med.* 285 (21) (1971) 1182–1186.
- [2] M. J. Gimbrone, S. Leapman, R. Cotran, J. Folkman, Tumor dormancy in vivo by prevention of neovascularization, *J. Experimental Med.* 136 (1972) 261–276.
- [3] A. Anderson, M. Chaplain, Continuous and discrete mathematical models of tumour-induced angiogenesis, *Bull. Math. Biol.* 60 (1998) 857–899.
- [4] M. Aubert, M. and Chaplain, S. McDougall, A. Devlin, C. Mitchell, A continuum mathematical model of the developing murine retinal vasculature, *Bull. Math. Biol.* 73 (2011) 2430–2451.
- [5] M. Bodnar, M. J. Piotrowska, U. Foryś, E. Nizińska, Model of tumour angiogenesis — analysis of stability with respect to delays, *Math. Biosci. Eng.* 10 (1) (2013) 19–35. doi : 10.3934/mbe.2013.10.19.
- [6] M. Chaplain, B. Sleeman, A mathematical model for the production and secretion of tumour angiogenesis factor in tumours, *IMA J. Math. Appl. Med. Biol.* 7 (1990) 93–108.
- [7] M. Chaplain, A. Stuart, A model mechanism for the chemotactic response of endothelial cells to tumour angiogenesis factor, *IMA J. Math. Appl. Med. Biol.* 10 (1993) 149–168.
- [8] A. d’Onofrio, A. Gandolfi, Tumour eradication by antiangiogenic therapy: analysis and extensions of the model by Hahnfeldt et al. (1999), *Math. Biosci.* 191 (2004) 159–184.
- [9] A. d’Onofrio, A. Gandolfi, The response to antiangiogenic anticancer drugs that inhibit endothelial cell proliferation, *Applied Mathematics and Computation* 181 (2006) 1155–1162.
- [10] A. d’Onofrio, A. Gandolfi, A family of models of angiogenesis and anti-angiogenesis anti-cancer therapy, *Math. Med. Biol.* 26 (2009) 63–95.
- [11] P. Hahnfeldt, D. Panigrahy, J. Folkman, L. Hlatky, Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy, *Cancer Res.* 59 (19) (1999) 4770–4775.
- [12] M. Chaplain, Blood flow and tumour-induced angiogenesis: Dynamically adapting vascular networks, in: T. Jackson (Ed.), *Modeling Tumor Vasculature: Molecular, Cellular and Tissue Level Aspects and Implications*, Springer: New York, 2012, Ch. 8, pp. 167–212.

- [13] M. Watson, S. McDougall, M. Chaplain, A. Devlin, C. Mitchell, Dynamics of angiogenesis during murine retinal development: a coupled in vivo and in silico study, *J.R. Soc. Interface* 9 (2012) 2351–2364.
- [14] M. Chaplain, A hybrid discrete-continuum model of tumor-induced angiogenesis, in: T. Jackson (Ed.), *Modeling Tumor Vasculature: Molecular, Cellular and Tissue Level Aspects and Implications*, ed., Springer: New York, 2012, Ch. 5, pp. 105–134.
- [15] S. McDougall, M. Watson, A. Devlin, C. Mitchell, M. Chaplain, A hybrid discrete-continuum mathematical model of pattern prediction in the developing retinal vasculature, *Bull. Math. Biol.* 74 (2012) 2272–2314.
- [16] M. Bodnar, U. Foryś, Three types of simple DDE's describing tumor growth, *J. Biol. Sys.* 15 (4) (2007) 1–19. doi:10.1142/S0218339007002313.
- [17] M. Bodnar, U. Foryś, Influence of time delays on the Hahnfeldt et al. angiogenesis model dynamics, *Appl. Math. (Warsaw)* 36 (3) (2009) 251–262.
- [18] A. d'Onofrio, Rapidly acting antitumoral antiangiogenic therapies, *Phys. Rev. E* 76 (2007) 031920. doi:10.1103/PhysRevE.76.031920.
- [19] A. Ergun, K. Camphausen, L. M. Wein, Optimal scheduling of radiotherapy and angiogenic inhibitors, *Bull. Math. Biol.* 65 (3) (2003) 407–424.
- [20] S. McDougall, A. Anderson, M. Chaplain, J. Sherratt, Mathematical modelling of flow through vascular networks: Implications for tumour-induced angiogenesis and chemotherapy strategies, *Bull. Math. Biol.* 64 (2002) 673–702.
- [21] M. Orme, M. Chaplain, Two-dimensional models of tumour angiogenesis and anti-angiogenesis strategies, *IMA J. Math. Appl. Med. Biol.* 14 (1997) 189–205.
- [22] J. Poleszczuk, M. Bodnar, U. Foryś, New approach to modeling of antiangiogenic treatment on the basis of Hahnfeldt et al. model, *Math. Biosci. Eng.* 8 (2) (2011) 591–603.
- [23] L. R. Sachs, R. K. and Hlatky, P. Hahnfeldt, Simple ode models of tumor growth and antiangiogenic or radiation treatment, *Math. Comput. Modelling* 33 (2001) 1297–1305.
- [24] U. Ledzewicz, H. Schättler, Antiangiogenic therapy in cancer treatment as an optimal control problem, *SIAM J. Control Optim.* 46 (2007) 1052–1079.
- [25] U. Ledzewicz, H. Schättler, Optimal and suboptimal protocols for a class of mathematical models of tumor anti-angiogenesis, *J. Theor. Biol.* 252 (2008) 295–312.
- [26] A. d'Onofrio, U. Ledzewicz, H. Maurer, H. Schättler, On optimal delivery of combination therapy for tumors, *Math. Biosci.* 222 (2009) 13–26. doi:10.1016/j.mbs.2009.08.004.
- [27] A. Świerniak, A. Gala, A. Gandolfi, A. d'Onofrio, Optimization of anti-angiogenic therapy as optimal control problem, in: *Proc: IASTED Biomechanics 2006* Actapress, 2006.
- [28] A. Świerniak, Comparison of six models of antiangiogenic therapy, *Appl. Math. (Warsaw)* 36 (3) (2009) 333–348.
- [29] A. Świerniak, Control problems related to three compartmental model of combined anti-cancer therapy, in: *Proceedings of the 20th Mediterranean Conference on Control & Automation (MED'12)*, 2012, pp. 1428–1433.

- [30] L. Arakelyan, Y. Merbl, Z. Agur, Vessel maturation effects on tumour growth: validation of a computer model in implanted human ovarian carcinoma spheroids, *European J. Cancer* 41 (2005) 159–167.
- [31] L. Arakelyan, V. Vainstein, Z. Agur, A computer algorithm describing the process of vessel formation and maturation, and its use for predicting the effects of anti-angiogenic and anti-maturation therapy on vascular tumor growth, *Angiogenesis* 5 (3) (2002) 203–214.
- [32] M. Bodnar, U. Foryś, Hahnfeldt angiogenesis model with time delays, in: *Proceedings of XIII National Conference on Application of Mathematics in Biology and Medicine*, 2007, pp. 18–23.
- [33] M. J. Piotrowska, U. Foryś, Analysis of the Hopf bifurcation for the family of angiogenesis models, *J. Math. Anal. Appl.* 382 (2011) 180–203. doi:10.1016/j.jmaa.2011.04.046.
- [34] U. Foryś, M. Piotrowska, Analysis of the Hopf bifurcation for the family of angiogenesis models II: the case of two nonzero unequal delays, *Appl. Math. Comput.* 220 (2013) 277–295.
- [35] V. Kolmanovskii, A. Myshkis, *Applied Theory of Functional Differential Equations*, Kluwer Academic Publishers, 1992.
- [36] S. Bernard, J. Bélair, M. Mackey, Sufficient conditions for stability of linear differential equations with distributed delay, *Discrete Contin. Dyn. Syst. Ser. B.* 1(2) (2001) 233–256.
- [37] S. A. Campbell, R. Jessop, Approximating the stability region for a differential equation with a distributed delay, *Math. Model. Nat. Phenom.* 4 (2) (2009) 1–27. doi:10.1051/mmnp/20094201.
URL <http://dx.doi.org/10.1051/mmnp/20094201>
- [38] G. Huang, Y. Takeuchi, R. Miyazaki, Stability conditions for a class of delay differential equations in single species population dynamics, *Discrete and Continuous Dynamical Systems - Series B* 17 (7) (2012) 2451–2464. doi:10.3934/dcdsb.2012.17.2451.
URL <http://aims sciences.org/journals/displayArticlesnew.jsp?paperID=7483>
- [39] G. Kiss, B. Krauskopf, Stability implications of delay distribution for first-order and second-order systems, *Discrete and Continuous Dynamical Systems - Series B* 13 (2) (2010) 327–345. doi:10.3934/dcdsb.2010.13.327.
URL <http://aims sciences.org/journals/displayArticlesnew.jsp?paperID=4791>
- [40] T. Faria, J. J. Oliveira, Local and global stability for Lotka-Volterra systems with distributed delays and instantaneous negative feedbacks, *J. Diff. Equations* 244 (5) (2008) 1049–1079. doi: <http://dx.doi.org/10.1016/j.jde.2007.12.005>.
URL <http://www.sciencedirect.com/science/article/pii/S002203960700410X>
- [41] A. d’Onofrio, F. Gatti, P. Cerrai, L. Freschi, Delay-induced oscillatory dynamics of tumour-immune system interaction, *Math. Comput. Model.* 51 (2010) 572–591.
- [42] Y. Hino, S. Murakami, T. Naito, *Functional Differential Equations with Infinite Delay*, Vol. 1473 of *Lecture Notes in Mathematics*, Springer-Verlag, New York, 1991.
- [43] J. Hale, S. Lunel, *Introduction to Functional Differential Equations*, Springer, New York, 1993.
- [44] Q. I. Rahman, G. Schmeisser, *Analytic Theory of Polynomials*, Oxford University Press, New York, 2002.

- [45] K. L. Cooke, P. van den Driessche, On zeroes of some transcendental equations, *Funkcj. Ekwacioj* 29 (1986) 77–90.
- [46] U. Foryś, Biological delay systems and the Mikhailov criterion of stability, *J. Biol. Sys.* 12 (1) (2004) 45–60.
- [47] P. Hahnfeldt, D. Panigrahy, J. Folkman, L. Hlatky, Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy, *Cancer Res.* 59 (19) (1999) 4770–4775.
- [48] G. A. Bocharov, F. A. Rihan, Numerical modelling in biosciences using delay differential equations, *J. Comput. Appl. Math.* 125 (2000) 183–199.
- [49] T. Erneux, *Applied delay differential equations*, Springer, 2009.
- [50] M. Bodnar, A. Bartłomiejczyk, Stability of delay induced oscillations in gene expression of Hes1 protein model, *Non. Anal. - Real.* 13 (5) (2012) 2228–2239. doi:10.1016/j.nonrwa.2012.01.017.
- [51] N. A. Monk, Oscillatory expression of Hes1, p53, and NF- κ B driven by transcriptional time delays, *Curr. Biol.* 13 (2003) 1409–1413. doi:10.1016/S0960-9822(03)00494-9.
- [52] M. J. Piotrowska, U. Foryś, M. Bodnar, J. Poleszczuk, A simple model of carcinogenic mutations with time delay and diffusion, *Mathematical Biosciences and Engineering* 10(3) (2013) 861–872.
- [53] M. J. Piotrowska, M. Bodnar, J. Poleszczuk, U. Foryś, Mathematical modelling of immune reaction against gliomas: sensitivity analysis and influence of delays, *Non. Anal. - Real.* 14 (2013) 1601–1620. doi:10.1016/j.nonrwa.2012.10.020.
- [54] U. Foryś, Marchuk's model of immune system dynamics with application to tumour growth, *J. Theor. Med.* 4 (1) (2002) 85–93.
- [55] M. Bodnar, U. Foryś, J. Poleszczuk, Analysis of biochemical reactions models with delays, *J. Math. Anal. Appl.* 376 (2011) 74–83. doi:10.1016/j.jmaa.2010.10.038.
- [56] J. Miękisz, J. Poleszczuk, M. Bodnar, U. Foryś, Stochastic models of gene expression with delayed degradation, *Bull. Math. Biol.* 73 (9) (2011) 2231–2247. doi:10.1007/s11538-010-9622-4.
- [57] K. Cooke, P. van den Driessche, X. Zou, Interaction of maturation delay and nonlinear birth in population and epidemic models, *J. Math. Biol.* 38 (1999) 332–352.
- [58] Y. Enatsu, Y. Nakata, Y. Muroya, Global stability of SIR epidemic models with a wide class of nonlinear incidence rates and distributed delays, *Discrete Contin. Dyn. Syst. Ser. B* 15 (1) (2011) 61–74. doi:10.3934/dcddb.2011.15.61.
- [59] M. C. Mackey, Unified hypothesis of the origin of aplastic anemia and periodic hematopoiesis, *Blood* 51 (1978) 941–956.
- [60] P. Fortin, M. C. Mackey, Periodic chronic myelogenous leukemia: Spectral analysis of blood cell counts and etiological implications, *Brit. J. Haematol.* 104 (1999) 336–345.
- [61] J. W. Uhr, T. Tucker, R. D. May, H. Siu, E. S. Vitetta, Cancer dormancy: Studies of the murine BCL₁ lymphoma., *Cancer Res. (Suppl.)* 51 (1991) 5045s–5053s.

- [62] R. Chignola, A. Schenetti, G. Andrighetto, E. Chiesa, R. Foroni, S. Sartoris, G. Tridente, D. Liberati, Forecasting the growth of multicell tumour spheroids: implications for the dynamic growth of solid tumours, *Cell Prolif* 33 (4) (2000) 219–229. doi:10.1046/j.1365-2184.2000.00174.x.
URL <http://dx.doi.org/10.1046/j.1365-2184.2000.00174.x>
- [63] R. Chignola, A. Schenetti, E. Chiesa, R. Foroni, S. Sartpris, A. Brendolan, G. Tridente, G. Andrighetto, D. Liberati, Oscillating growth patterns of multicellular tumour spheroids, *Cell Proliferation* 32 (1) (2003) 39–48. doi:10.1046/j.1365-2184.1999.3210039.x.
URL <http://dx.doi.org/10.1046/j.1365-2184.1999.3210039.x>
- [64] V. A. Kuznetsov, I. A. Makalkin, M. A. Taylor, A. S. Perelson, Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis, *Bull. Math. Biol.* 56 (2) (1994) 295–321. doi:10.1007/bf02460644.
- [65] D. Kirschner, J. Panetta, Modeling immunotherapy of the tumor-immune interaction, *J. Math. Biol.* 37 (3) (1998) 235–252. doi:10.1007/s002850050127.
- [66] L. Pujo-Menjouet, S. Bernard, M. C. Mackey, Long period oscillations in a g 0 model of hematopoietic stem cells, *SIAM J. Appl. Dyn. Syst.* 4 (2) (2005) 312–332. doi:10.1137/030600473.
URL <http://dx.doi.org/10.1137/030600473>
- [67] S. Bernard, J. Bélair, M. C. Mackey, Bifurcations in a white-blood-cell production model, *Comptes Rendus Biologies* 327 (3) (2004) 201–210. doi:10.1016/j.crvi.2003.05.005.
URL <http://dx.doi.org/10.1016/j.crvi.2003.05.005>
- [68] H. M. Byrne, The effect of time delays on the dynamics of avascular tumour growth, *Math. Biosci.* 144 (1997) 83–117.
- [69] U. Foryś, M. Bodnar, Time delays in proliferation process for solid avascular tumour, *Math. and Comp. Modelling* 37 (11) (2003) 1201–1209.
- [70] U. Foryś, M. Bodnar, Time delays in regulatory apoptosis for solid avascular tumour, *Math. and Comp. Modelling* 37 (11) (2003) 1211–1220.
- [71] M. J. Piotrowska, Hopf bifurcation in a solid avascular tumour growth model with two discrete delays, *Math. and Comp. Modelling* 47 (2008) 597–603.
- [72] D. Lane, p53, guardian of the genome, *Nature* 358 (1992) 15–16.
- [73] S. Bernard, B. Cajavec, L. Pujo-Menjouet, M. C. Mackey, H. Herzel, Modelling transcriptional feedback loops: the role of gro/tle1 in hes1 oscillations, *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* 364 (1842) (2006) 1155–1170. doi:10.1098/rsta.2006.1761.
URL <http://dx.doi.org/10.1098/rsta.2006.1761>